BRIEFING BOOK

ONCOLOGY DRUGS ADVISORY COMMITTEE MEETING

NDA 22-374

OMAPRO™ (omacetaxine mepesuccinate)

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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1 EXECUTIVE SUMMARY

Omacetaxine is a first-in-class cetaxine that functions as a protein translation inhibitor and is an important addition to the therapeutic armamentarium of agents for the treatment of chronic myelogenous leukemia (CML). Omacetaxine specifically addresses an unmet medical need in patients with the T315I mutation that renders their disease resistant to approved tyrosine kinase inhibitor (TKI) agents (Gleevec® [imatinib mesylate], Sprycel® [dasatinib], Tasigna® [nilotinib hydrochloride monohydrate]).

The CML T315I patient has no effective treatment options and there is an immediate need for a proven therapy. Failure to treat these patients will lead to disease progression and shortened life expectancy. Treatment of the CML T315I patients with omacetaxine has proven effective. In the largest study ever conducted in CML patients with the T315I mutation (study CML-202), chronic phase CML patients treated with omacetaxine achieved durable hematologic and cytogenetic responses with a rapid onset, and in advanced disease phases (accelerated phase and blast phase) patients achieved high rates of complete hematologic response. For two of the chronic phase CML patients who achieved a major cytogenetic response, allogeneic hematopoietic stem cell transplantation became a therapeutic option. Treatment with omacetaxine also induced major molecular responses in patients who had achieved a complete cytogenetic response. The overall survival data from study CML-202 exceeds that from the literature.

Omacetaxine treatment at twice daily dose of 1.25 mg/m^2 was well tolerated by patients in the pivotal and supportive CML studies. The main safety issue was myelosuppression, a recognized complication of CML therapy, an anticipated on-target effect of omacetaxine, and an anticipated adverse event in heavily pretreated patients. Dose delays due to myelosuppression were common, occurring more frequently during the early more intensive treatment cycles. Management of myelosuppression was readily achieved by adjustment of the number of dosing days per treatment cycle. Non-hematologic toxicities were less common and generally mild to moderate in severity.

The Oncologic Drugs Advisory Committee (ODAC) has been requested to evaluate omacetaxine mepesuccinate for the following indication:

> OMAPRO™ (omacetaxine mepesuccinate) is indicated for the treatment of adults with chronic myeloid leukemia who have failed prior therapy with imatinib and have the Bcr-Abl T315I mutation.

The primary basis of this filing is the Phase 2, open-label CML-202 study conducted in CML patients who had failed imatinib therapy and have the Bcr-Abl T315I mutation. Study CML-202 has enrolled 66 CML T315I patients and is the largest prospectively designed trial of CML patients with the T315I mutation. Data from study CML-202 are supported by study CML-203, a 65-patient study of omacetaxine in CML patients who had failed therapy with two or more TKIs.

1.1 History of Omacetaxine

Omacetaxine (formerly known as homoharringtonine or HHT) has been studied in the clinic for over 30 years. There is now a significant body of data in the literature that demonstrates the clinical benefit of omacetaxine in the treatment of CML and other hematologic malignancies. Over 1,500 patients, including 460 CML patients, have been treated with omacetaxine in more than 30 published clinical trials.

The clinical utility of omacetaxine was demonstrated in CML patients during the 1980s and 1990s; however, following the successful introduction of imatinib mesylate (Gleevec®) for the treatment of CML in 2001, interest in the development of omacetaxine declined.

1.2 Overview of CML

CML is caused by a reciprocal translocation between chromosomes 9 and 22, leading to the development of a fusion gene and the resulting synthesis of the constitutively activated tyrosine kinase, Bcr-Abl. CML has three phases representing a disease continuum: chronic (CML-CP), accelerated (CML-AP), and blast phase (CML-BP). CML is treated with TKIs which have selective activity against Bcr-Abl. TKIs are effective CML therapies that induce high response rates in both the front-line and second-line settings. Imatinib is the current standard of care for the treatment of frontline CML. The predicted median survival for CML-CP patients is now greater than 10 years from diagnosis. Patients who develop resistance or intolerance to imatinib are treated with the second generation TKI drugs dasatinib and nilotinib.

Point mutations in the Abl kinase domain of Bcr-Abl are the most commonly reported cause of imatinib resistance, representing 50 to 80% of patients with imatinib failure. Point mutations lead to amino acid substitutions that interfere with binding of imatinib. The second generation compounds, dasatinib and nilotinib, have increased binding affinity to the Abl kinase domain over imatinib and subsequently have activity against many of the imatinib-resistant kinase domain mutants. None, however, are effective against one particular mutation, T315I.

1.3 The Medical Need of the CML T315I Patient

All TKI-treated CML patients will become resistant to further TKI therapy if they develop the specific Bcr-Abl kinase domain mutation, T315I. Replacement of threonine with isoleucine at position 315 (T315I) in the Abl kinase domain blocks the binding of all three approved TKIs to the ATP-binding site and leads to drug resistance. Treatment of CML patients with the T315I mutation by any of these TKI then leads to selection of the resistant CML cells, and an increasing proportion of the total burden of CML cells will contain the T315I mutation.

An estimated 250 to 300 CML patients are diagnosed with the T315I mutation per year in the US, and the incidence is expected to increase as dasatinib and nilotinib are more widely used. The presence of the T315I mutation has been associated with a poor prognosis. In contrast to the 10 year survival for patients with CML-CP treated with imatinib, the patient with the T315I mutation has a survival of 22 months from the time the mutation is detected.

With the exception of stem cell transplantation, there are currently no effective therapies for CML with the T315I mutation. Patients unsuitable for transplantation are managed with agents such as hydroxyurea (HU) that provide supportive care but do not prolong survival. As such, CML patients with the T315I mutation have a poor prognosis and an unmet medical need which requires a proven therapy.

1.4 Product Rationale

Omacetaxine is a reversible protein translation inhibitor that is active against Mcl-1, an important regulator of lymphocytic and hematopoietic stem cell survival, leading to apoptosis in leukemic cell lines. Unlike the TKIs, omacetaxine does not depend on Bcr-Abl binding for its activity and its activity is independent of the mutational status of Bcr-Abl. Omacetaxine has demonstrated in vitro activity against a wide variety of leukemic cell lines and against Ba/F3 cell lines expressing Bcr-Abl with the T315I Abl kinase domain mutation.

This activity of omacetaxine was initially evaluated in a clinical study of CML-AP patients (Study 04.2/04.3) in which CML patients with the T315I mutation responded to therapy with hematologic and cytogenetic responses. The pivotal study CML-202 was designed to confirm the efficacy and safety of omacetaxine in the CML T315I population.

1.5 Clinical Efficacy

Since no approved drug therapy is effective in CML patients with the Bcr-Abl T315I mutation, ChemGenex conducted a non-randomized, open-label study to evaluate the safety and efficacy of omacetaxine in this condition. CML-202 is a single-arm study in patients who had failed imatinib therapy and tested positive for the T315I mutation. Data collected from this pivotal study provide clear evidence of efficacy of omacetaxine in the proposed indication.

Omacetaxine was administered at a dose of 1.25 mg/m^2 subcutaneously (SC) twice daily for 14 days of a 28-day cycle. Upon achievement of a hematologic response, the dose schedule was modified to 7 days of administration in each 28-day cycle for up to two years.

Major cytogenetic response is an accepted surrogate for prolonged survival and was used as the basis of the approvals for imatinib, dasatinib, and nilotinib. For CML-AP and CML-BP, hematologic responses are considered the primary endpoints that are predictive of clinical benefit.

The primary endpoints were the proportion of patients achieving the following responses:

CML-CP patients:	Major cytogenetic response (MCyR) or complete hematologic response (CHR)
CML-AP or CML-BP patients:	CHR, no evidence of leukemia (NEL), or return to chronic phase (RCP)

A MCyR was achieved by ten CML-CP patients (25.0%, one-sided 95% lower CI, 12.7%) with six achieving a CCyR and four achieving a PCyR (Table 1). The median duration of

MCyR could not be estimated; however, the response was ongoing in 8 of the 10 patients at the time of data cut-off or patient discontinuation from study. Two of these patients discontinued to receive an hematopoietic stem cell transplant. The CHR rate in CML-CP patients was 85%. The median duration of CHR in this group was 18.7 months (95% confidence interval [CI], 11.1, NA). In CML-AP patients, 37.5% of patients achieved an overall hematologic response (Table 1). One (6.3%) CML-AP patient achieved a MCyR (complete) after 2.8 months on study. Hematologic response rates in CML-BP patients were lower.

In most patients, CHR was usually achieved within the first cycle (1 month). CML-CP patients who achieved a MCyR did so within 1.7 to 7.8 months (median 4.9 months) of treatment. These results demonstrate that omacetaxine is an effective and durable therapy with rapid onset of action for CML patients with the Bcr-Abl T315I mutation.

Table 1. Efficacy of Omacetaxine in Study CML-202

Response Category	CML-CP n = 40	CML-AP n = 16	CML-BP n = 10
	Patients, n (%)		
Cytogenetic			
MCyR	10 (25.0)	1 (6.3)	0
CCyR	6 (15.0)	1 (6.3)	0
PCyR	4 (10.0)	0	0
Hematologic			
Overall HR	34 (85.0)	6 (37.5)	3 (30.0)
CHR	34 (85.0)	5 (31.3)	2 (20.0)
RCP	NA	1 (6.3)	1 (10.0)

MCyR = major cytogenetic response; CCyR = complete cytogenetic response; PCyR = partial cytogenetic response; HR = hematologic response; CHR = complete hematologic response; RCP = return to chronic phase

1.6 Clinical Safety

Overall, safety data were collected from 212 patients administered SC omacetaxine in six independent studies (Table 3). To characterize the safety profile of omacetaxine in CML patients, a pooled analysis of safety data from the 131 patients enrolled in the studies CML-

202 and CML-203 (CML safety cohort) are reported in this document. These two studies were identical in design and utilized the proposed product label dosing schedule and the subcutaneous route of administration.

Patients in the CML safety cohort had been previously treated for their CML for long periods of time, with a median time from initial CML diagnosis to screening of 54 months. Many of the patients had failed CML treatment with multiple therapies including TKIs, IFN-α and chemotherapy. Within the CML safety cohort, the most common adverse events – thrombocytopenia (60%), anemia (49%), and neutropenia (38%) – were predictable, generally tolerable, reversible, and managed by reducing the number of dosing days per cycle or delaying dosing. Nadir values were typically reached within 2 to 3 weeks after the first dose of each cycle, and recovery of blood counts generally occurred within 1 to 3 weeks of the nadir. Non-hematologic adverse events were generally mild to moderate and consisted mostly of diarrhea (43%), fatigue (31%), pyrexia (30%), nausea (28%), asthenia (21%), and headache (19%). There were five deaths attributed to omacetaxine treatment (three due to sepsis, one due to febrile neutropenia, and one with unknown cause).

1.7 Benefit/Risk Conclusions

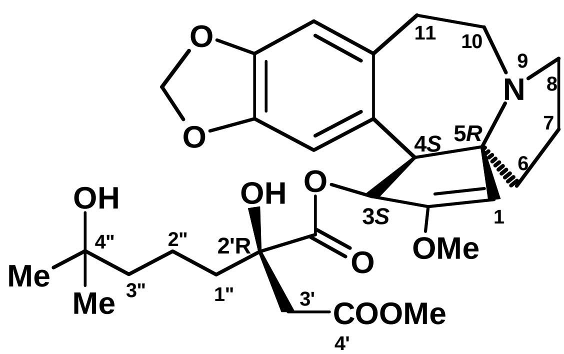
In conclusion, omacetaxine offers an important therapeutic option for the treatment of CML patients who have the T315I mutation, a population that has a clear unmet medical need and no proven treatment options. In study CML-202, CML-CP patients treated with omacetaxine achieved durable hematologic and cytogenetic responses with a rapid onset, and in advanced disease phase patients (CML-AP and CML-BP) achieved high rates of CHR. For two patients who achieved MCyR, hematopoietic stem cell transplantation (HSCT) became a therapeutic option. The main safety finding was myelosuppression, a recognized complication of CML therapy and an anticipated adverse event in these heavily pre-treated patients. The myelosuppression was predictable, generally tolerable, reversible, and managed by adjusting the number of dosing days per cycle. Non-hematologic toxicities were generally mild to moderate in severity and typically not dose limiting. Overall, omacetaxine demonstrated an acceptable benefit-to-risk ratio in heavily pretreated patients who have a poor prognosis and no proven treatment options.

2 PRODUCT INFORMATION

- **Omacetaxine mepesuccinate** (omacetaxine) is:
  - A protein translation inhibitor
  - A semisynthetic version of a plant alkaloid extracted from *Cephalotaxus fortunei*, a species of evergreen that is indigenous to China
  - A first-in-class cetaxine

- **Chemical name:** Cephalotaxine, 4′-methyl (2′R)-hydroxyl-2′-(4″-hydroxyl-4″-methylpentyl) butanedioate (ester), [3(R)]

- **Chemical structure**



- **Drug product:** omacetaxine mepesuccinate for injection is supplied as a lyophilized powder that is reconstituted with 1.0 mL 0.9% isotonic saline (NaCl) immediately prior to use

- **Recommended dose:** 1.25 mg/m^2 administered twice daily by SC injection

- **Proposed indication:** OMAPRO™ (omacetaxine mepesuccinate) is indicated for the treatment of adults with chronic myeloid leukemia who have failed prior therapy with imatinib and have the Bcr-Abl T315I mutation

3 BACKGROUND

Chronic myeloid leukemia (CML) is a hematopoietic stem cell disorder that is associated with a reciprocal translocation between chromosomes 9 and 22, producing the Philadelphia (Ph) chromosome[1]. This Ph chromosome results in the creation of a fusion gene that in turn results in the synthesis of the chimeric protein Bcr-Abl, a constitutively active form of the Abl tyrosine kinase[2]. CML has three phases representing a disease continuum: chronic (CML-CP), accelerated (CML-AP), and blast phase (CML-BP). Typically patients present in chronic phase and progress to accelerated and then blastic phases as the number of blasts in the blood and bone marrow increases.

The clinical efficacy of CML treatments are assessed using established and widely accepted criteria of hematologic and cytogenetic response. Hematologic responses are mainly assessed using blood count criteria. Cytogenetic responses are assessed by examining bone marrow cells for the presence (or absence) of the Ph chromosome, a surrogate marker of disease burden. A major cytogenetic response (MCyR) is achieved when 35% or less of cells contain the Ph chromosome. Achievement of a MCyR has been associated with an improved survival since the pre-TKI era and thus has been used as the surrogate endpoint for the approval of drugs for the treatment of CML including imatinib, dasatinib and nilotinib[3-5]. For CML-AP and CML-BP, hematologic responses are considered the primary endpoints that are predictive of clinical benefit[3-5].

Before the introduction of imatinib therapy, the treatment options available to CML patients included conventional therapy, such as radiation and cytotoxic agents (hydroxyurea [HU] or busulfan), treatment with interferon (IFN-α) or, for younger patients with HLA-matched donors, allogeneic stem cell transplantation. With conventional therapy, cytogenetic responses were rarely seen[6, 7]. The disease was thus nearly universally fatal with a median overall survival of 4 to 5 years for CML-CP patients. Progression to acceleration was inevitably followed by an aggressive period of blast crisis, unresponsive to all forms of chemotherapy and rapidly fatal (1-3 months)[6-8].

The introduction of IFN-α replaced conventional therapy. Randomized studies of newly diagnosed chronic phase patients demonstrated MCyR rates of up to 30% for patients treated with IFN-α (as a single agent or in combination with chemotherapy) in contrast to rates of less than 1% in patients treated with HU or busulfan alone[6, 7]. Median survival for all chronic phase patients increased to 5 to 6 years. However, despite the initial successes with IFN-α, the majority of patients developed resistance or intolerance to the drug[6, 7].

3.1 Tyrosine Kinase Inhibitor Therapy Advanced the Treatment of CML

The introduction of imatinib in 2001 revolutionized the treatment of CML patients with the achievement of high rates of hematologic and cytogenetic responses (in both front-line and interferon refractory patients)[9]. Imatinib was developed to block the kinase activity of Bcr-Abl, thereby eliminating the proliferative and anti-apoptotic signals instigated by this chimeric protein[10]. Known as Gleevec®, imatinib became the standard of care for first-line treatment of CML[10-12]. After five years of imatinib therapy, 87% of chronic phase patients achieved a complete cytogenetic response (no Ph+ cells on cytogenetic analysis of the bone marrow) with an overall survival of nearly 90%[10]. The predicted median survival for CML-CP patients is now greater than 10 years from diagnosis[9]. For patients newly presenting in accelerated and blast phase, survival on imatinib is of the order of 3 to 4 years and 7 months, respectively[13, 14]. Some patients are unable to tolerate imatinib and many develop imatinib-resistant forms of CML. Current estimates suggest that 30 to 40 per cent of CML-CP patients who receive imatinib as first line therapy discontinued treatment within 7 years and require alternative forms of treatment[10, 11, 15].

A number of reasons for imatinib resistance have been proposed, including amplification of the Bcr-Abl fusion gene, over expression of Bcr-Abl protein, or decreased cellular bioavailability of imatinib.[16-18] However, the most commonly reported cause of imatinib resistance is the development of point mutations in the Abl kinase domain of Bcr-Abl[19, 20]. Fifty to 80% of patients who are resistant to imatinib therapy have point mutations. Point mutations lead to amino acid substitutions that interfere with the binding of imatinib. There are over 90 different mutations reported in the literature.

In 2006 and 2007, the second generation TKIs, dasatinib and nilotinib, were approved for patients who had resistance or were intolerant to imatinib treatment. These TKIs have increased binding affinity to the Abl kinase domain compared to imatinib and subsequently have activity against many of the imatinib-resistant kinase domain mutants[21, 22]. The NDA approvals for dasatinib and nilotinib were based on data from non-comparative studies using hematologic and major cytogenetic response endpoints. In a pivotal single-arm study of 186 imatinib-resistant or -intolerant CML-CP patients, dasatinib administered once daily induced 90% CHR and 45% MCyR[23]. In a pivotal single-arm study of 232 imatinib-resistant or -intolerant CML-CP patients using nilotinib twice daily, a 40% unconfirmed MCyR rate was observed[24].

3.2 The Bcr-Abl T315I Mutation

Both dasatinib and nilotinib are effective against most mutations when tested in the laboratory. The in vitro potency of these TKIs correlates well with their efficacy in patients with the corresponding mutations after imatinib failure. Notably one mutation, the T315I mutation, does not respond to any approved TKI in vitro. Likewise, patients with this mutation do not respond to therapy with any of the approved TKIs. Thus, the presence of the T315I mutation is associated with a poor overall prognosis determined mostly by the lack of effective therapy. CML patients with the T315I mutation have an urgent need for a safe and effective therapy.

The T315I mutation was first described by Gorre et al., in 2001[16]. Using biochemical and molecular techniques, it was shown that six out of nine patients who had relapsed on imatinib carried the T315I mutation[16]. The mechanism for this resistance to imatinib treatment was elucidated from the crystal structure of the catalytic domain of Abl complexed to a variant of imatinib. Based on this model, it was predicted that the replacement of the threonine with isoleucine at position 315 (T315I) in the Abl kinase domain causes a steric hindrance to the binding of imatinib to the ATP-binding site.

In clinical studies of CML patients who were resistant or intolerant to imatinib, patients with the T315I mutation at baseline did not respond to dasatinib or nilotinib therapy[25, 26,22]. The lack of efficacy of the second generation TKIs in these patients has been attributed to the same structural constraints imposed by the T315I mutation affecting imatinib binding to the Abl kinase[25, 26].

Because of the ineffectiveness of the available TKIs against T315I, there is some selection for cells containing this mutation among patients treated with sequential TKIs. The emergence of mutations following treatment of CML cells with TKIs in vitro was induced by using an assay where Ba/F3-p210$^{BCR\text{-}ABL}$ cells were chemically mutagenized with *N*-ethyl-*N*-nitrosourea and then exposed to TKIs[27]. The one common mutation observed with all TKI in this system is T315I. After imatinib exposure the most frequent mutations identified were T315I (37%) and Y243H (45%). After dasatinib and nilotinib exposure, the T315I mutation occurred at the highest frequency for all mutations, 78% and 51%, respectively.

Consistent with the in vitro data, the T315I mutation is the most common mutation identified in imatinib-resistant CML patients, occurring in up to 20% of these CML patients[28-30]. The emergence of the T315I mutation in CML patients treated with second generation TKIs (who do not have the T315I mutation at baseline) appears to be more common, with up to 40% of patients developing resistance to TKI therapy after acquiring the T315I mutation[31, 32]. Overall, an estimated 250 to 300 CML patients are diagnosed with the T315I mutation per year in the US and the incidence is expected to increase as dasatinib and nilotinib are more widely used.

The laboratory and clinical experience with the T315I mutation clearly demonstrates the need for new approaches to treat CML T315I patients. One approach is to use drugs with a mechanism of action that is not dependent on Abl kinase inhibition.

3.3 The Medical Need of the CML T315I Patient

Most patients with CML have effective therapy available both as initial therapy and as salvage for those who experience resistance or intolerance of the first-line approach. In contrast, CML patients with the T315I mutation do not have effective treatments available to them. Most receive supportive care with HU and a limited number of patients will have the option to receive allogeneic hematopoietic stem cell transplantation (HSCT).

HU is an antineoplastic agent that inhibits the enzyme ribonucleotide reductase. HU may achieve hematologic responses in some patients, but only rarely will achieve a major cytogenetic response, a response that is required for prolonged survival[33, 34]. Furthermore, HU does not control Bcr-Abl T315I levels in CML-AP patients with the mutation[35]. In clinical practice, HU is not considered a long term strategy for treating patients with CML and is currently used temporarily to control high blood counts in CML T315I patients with variable success. As described later in this document (see Section 8.1.1), half of the CML-CP patients who entered the pivotal CML T315I study (study CML-202) were receiving HU therapy without having achieved adequate control of peripheral blood counts.

IFN-α is approved for use in CML-CP patients who are minimally pretreated (within 1 year of diagnosis). As most patients with the T315I mutation are in late chronic phase or have more advanced disease, the clinical benefit of IFN-α in this patient population is not clear. There are no published data on the clinical effectiveness of HU or interferon in the treatment of CML T315I patients.

At the present time allogeneic HSCT remains the only potentially curative treatment in CML. Widespread application of this modality is limited by donor availability and the high toxicity associated with the procedure. For CML-CP patients who are under the age of 55–60 years and eligible for allogeneic HSCT, the three-to-five year survival rate is 40–80%. There are no published data on the safety and efficacy outcomes of HSCT in the CML T315I population[36]. In light of the curative potential of HSCT transplantation, patients eligible for transplantation were excluded from enrollment in the pivotal CML T315I study (study CML-202).

The poor prognosis for CML T315I patients has been described in several retrospective clinical studies of these patients[37,38,39]. These studies concluded that: a) the T315I mutation is associated with poor overall survival compared to that seen in patients harboring other mutations[38], b) survival of patients with the T315I mutation is mostly dependant on the stage of disease at the time of detection of the mutation[39], and c) on initial detection of the T315I mutation, patients should rapidly switch from TKI to alternative therapy[37].

The largest of these retrospective studies was a multicenter epidemiological study of 222 patients with CML and the T315I mutation[37]. After T315I mutation detection, multiple therapies were used to treat patients, including imatinib, dasatinib, nilotinib, HU, cytarabine, HSCT, and IFN-α . Response rates with these agents were not reported. From the time of T315I mutation detection, the overall survival was 22.4 months in CML-CP patients, 28.4 months in CML-AP patients, and 4.0 months in CML-BP patients. The one year overall survival rates were 71% for CML-CP, 69% for CML-AP, and 23% for CML-BP patients. Overall survival data following therapeutic intervention (i.e. HU) for the T315I mutant were not reported. These relatively poor survival data are in marked contrast to the survival outcomes for CML patients without the T315I mutation who are receiving TKI therapy.

In summary, over the last decade advances have been made in the treatment of front-line CML using imatinib. The subsequent emergence of imatinib resistance has been successfully managed in approximately half of these patients by the introduction of the second generation TKIs, which are able to overcome the drug resistance resulting from most kinase domain mutations, with the exception of the T315I mutation. As a result, the CML T315I patient has very limited treatment options and an urgent need for an effective therapy for a life-threatening illness. There is a clear unmet medical need, as the lack of treatment options leads to disease progression and shortened life expectancy.

4 HISTORY OF OMACETAXINE

Omacetaxine (formerly known as homoharringtonine or HHT) has been studied in the clinic for over 30 years. There is now a valuable body of data in the literature that is indicative of its benefits in CML and other hematologic malignancies. Over 1,500 patients, including 460 CML patients, have been treated with omacetaxine in more than 30 published clinical trials.

Development Overview

In the 1980s and 1990s, the clinical utility of omacetaxine was demonstrated in patients with CML; however, following the successful introduction of imatinib mesylate (Gleevec®) for the treatment of CML in 2001, interest in the development of omacetaxine declined. The data provided here demonstrate the clinical effectiveness of omacetaxine in treating CML before the introduction of the TKIs and before the discovery of the T315I mutation.

The earliest publications on the clinical use of omacetaxine originated from China in the 1970s. As early as 1975, Chinese herbal medicine formulations containing homoharringtonine demonstrated anti-leukemia activity in patients with acute myeloid leukemia and acute lymphocytic leukemia[40]. In the US, the National Cancer Institute (NCI) opened the first IND for omacetaxine under the name homoharringtonine in 1981. Under this IND, studies were conducted using omacetaxine as a single agent and in combination with other therapies, including ara-C and IFN-α.

Initially, the drug was administered by bolus intravenous injection and was associated with acute cardiotoxicity. The introduction of continuous infusion schedules resulted in an improved safety profile with minimal cardiac toxicity. The later development of subcutaneous administration schedules resulted in further improvements in the safety profile and offered patients the convenience of home administration. The dose limiting toxicity was myelosuppression.

ChemGenex selected a 1.25 mg/m^2 twice daily subcutaneously administered dosing schedule for its pivotal and supportive CML studies based on the accumulated and extensive experience with the drug over the many years of clinical development. The final schedule was successfully piloted in clinical studies[41, 42] before it was adopted by ChemGenex.

The following is a summary of some of the early data on the efficacy and safety from studies conducted in CML including both the intravenous (IV) and subcutaneous (SC) routes of administration. The data demonstrates the clinical benefit of omacetaxine therapy for the treatment of CML before imatinib and the other TKIs were introduced.

Efficacy

Two studies conducted in the 1990s evaluated intravenously administered omacetaxine as a single agent in patients with CML (Table 2). In late CML-CP (diagnosis to treatment > 12 months), patients received induction treatment with omacetaxine 2.5 mg/m^2 daily by continuous infusion for 14 days every 4 weeks until a complete hematologic response was achieved, and then maintenance therapy with omacetaxine 2.5 mg/m^2 daily for 7 days every month[43]. The median number of courses administered was six. Of the 71 patients treated with omacetaxine, 42 (72%) achieved a CHR and 11 (15%) achieved a MCyR (which was a CCyR in 7% of patients). A second trial studied patients in early CML-CP (treatment within 12 months from diagnosis)[44]. Patients received six cycles of omacetaxine at the induction-maintenance schedule of the previous trial, followed by IFN-α maintenance therapy at a targeted dose of 5 MU/m^2 SC daily for as long as they were on study. Among 90 patients treated, 83 (92%) achieved CHR with MCyR in 24 (27%) of patients.

Table 2. Summary of Intravenously Administered Omacetaxine Therapy in CML-CP Patients

Reference	Therapy	No. of Patients	CHR (%)	MCyR (%)
Late CML-CP				
O'Brien, et al.[43]	OM	71	72	15
Kantarjian, et al.[45]	OM + ara-C	100	72	15
Early CML-CP				
O'Brien, et al.[44]	OM	90	92	27
O'Brien, et al.[46]	OM + IFN-α	37	89	43

Early CML-CP (treatment within 12 months from diagnosis); Late CML-CP (diagnosis to treatment > 12 months); CHR = complete hematologic response; OM = omacetaxine; ara-C = cytosine arabinoside; IFN-α = interferon-alpha.

In addition to single agent studies, intravenously administered omacetaxine was also combined with other commonly used agents in CML, i.e. ara-C and IFN-α. In a study combining omacetaxine plus low-dose ara-C in late CML-CP patients, patients received omacetaxine 2.5 mg/m^2/day by continuous infusion plus ara-C 15mg/m^2 daily in two SC doses, both given for 5 days every month[45]. While the CHR and cytogenetic response rates were identical to those reported in the omacetaxine alone study[43], omacetaxine plus ara-C was associated with a significant survival advantage (4-year survival rate of 58% versus 38%; [p=0.02]), which was confirmed by subset risk group analysis, and by multivariate analysis.[45] The combination of omacetaxine and IFN-α resulted in an improved MCyR rate of 43%[46].

An early Phase 1 study was conducted to evaluate the SC dosage form of omacetaxine. Seventeen patients with CML were treated with omacetaxine: 11 in the Phase 1 portion of the study (SC omacetaxine 0.5, 1.0 or 1.25 mg/m^2 twice daily) and six in the Phase 2 portion of the study (SC omacetaxine 1.25 mg/m^2 twice daily). The Phase 1 portion of the study determined that the dose of 1.25 mg/m^2 was well tolerated and the dose was selected as the dose for the Phase 2 portion of the study where six patients were accrued. All six were in late stage CML-CP with 100% Ph+ metaphases at study entry and had failed a median of five therapies, including imatinib (n = 5), IFN-α (n = 5), ara-C (n = 2), and farnesyl transferase inhibitors (n = 1). Patients were initially treated with an induction dosing schedule of omacetaxine 1.25 mg/m^2 SC twice daily for 14 days every 28 days until remission, followed by a maintenance schedule of omacetaxine 1.25 mg/m^2 SC twice daily for 7 days every 28 days. Of the five evaluable patients, all achieved CHR and were started on SC omacetaxine maintenance therapy after two cycles of induction therapy. Futhermore, one patient achieved a complete cytogenetic response (CCyR), and three achieved minor cytogenetic responses.

A Phase 1 study was completed of SC omacetaxine in patients with CML in accelerated or blast phases[41]. The maximum tolerated dose (MTD) was 1.25 mg/m^2 SC twice daily. The cohort was then expanded to treat patients in late chronic phase CML after imatinib failure at the MTD. Therapy consisted of an IV loading dose of omacetaxine 2.5 mg/mg^2 over 24 hours, followed by 1.25 mg/m^2 SC twice daily for 14 days every 28 days until remission, then for 7 days every 28 days. CHR was achieved in all 5 evaluable patients and 3 patients had cytogenetic responses: 1 complete and 2 minor.

Safety

In the early studies of omacetaxine utilizing a bolus or short IV infusion dose schedule, dose-limiting toxicities were primarily due to cardiovascular (arrhythmias and hypotension) and gastrointestinal adverse events (diarrhea, vomiting)[47]. Researchers determined that by lowering the doses and using longer exposure schedules, the extent and severity of these events was reduced, at which point myelosuppression became the more frequent dose-limiting toxicity[48-50]. Hypotension, although still observed, was controlled or reversed by temporary interruption of the infusion allowing most patients to complete their course of treatment. When dosed with a slow infusion, the safety profile consisted primarily of myelosuppression; other events, including fever, fatigue, asthenia, nausea and vomiting, tachycardia, and headache, were reduced and were not found to be dose limiting.

In the Phase 1 studies using the SC route of administration[41, 42], myelosuppression (grade 3/4 neutropenia, anemia, and thrombocytopenia) was reported by a majority of patients. Non-hematologic toxicities included grade 3/4 neutropenic fever, non-neutropenic fever, and fatigue. Importantly, the previously seen cardiac and gastrointestinal toxicities were not observed.

In summary, omacetaxine has been studied for over 30 years as a treatment for CML. However, following the successful introduction of imatinib for the treatment of CML in 2001, interest in the development of omacetaxine declined. Data from the literature demonstrate the clinical effectiveness of omacetaxine in treating CML in the pre-imatinib era. The safety profile of omacetaxine has been well described following the treatment of over 1,500 patients. Myelosuppression is the dose-limiting toxicity for the SC route of administration. Taken together with data collected from the clinical studies conducted by ChemGenex, an extensive body of evidence exists for the assessment of the benefit/risk profile of omacetaxine.

5 NONCLINICAL DEVELOPMENT

5.1 Mechanism of Action and Preclinical Activity

Omacetaxine is a reversible inhibitor of protein elongation that acts by inhibiting the early steps in polypeptide chain elongation involving aminoacyl-tRNA binding and peptide bond formation[51, 52]. In vitro, omacetaxine mediates inhibition of the Mcl-1, an important regulator of lymphocytic and hematopoietic stem cell survival, leading to apoptosis in leukemic cell lines[53]. Omacetaxine also decreases the levels of cyclin D1 and Myc-C[54], proteins involved in cell cycle regulation, and has been shown to be an inhibitor of murine and human Bcr-Abl-positive bone marrow leukemic progenitor cells[55, 56].

Omacetaxine is active in vitro against a wide variety of leukemic cell lines, irrespective of their lymphoid and myeloid origins, including murine leukemic stem cells[57]. Importantly, omacetaxine is active against murine lymphoid Ba/F3 cell lines that have been transfected to express Bcr-Abl with the T315I Abl kinase domain mutation[58]. Unlike the TKIs, omacetaxine does not depend on Bcr-Abl binding for its activity and its activity is independent of the mutational status of Bcr-Abl.

5.2 Toxicology

Omacetaxine was extensively tested in nonclinical in vitro and in vivo toxicology studies. The nonclinical toxicity profile of omacetaxine is consistent with the antiproliferative pharmacological activity of the drug, primarily affecting lymphoid, hematopoietic, and gastrointestinal systems. The toxicities were generally slow in onset and reversible upon cessation of dosing. The data support the use of omacetaxine for twice daily SC administration in humans. The potential for cardiac effects was carefully assessed in animal experiments. In vitro and in vivo studies did not demonstrate any potential for QT prolongation. These studies included an in vitro hERG assay, a Purkinje fiber assay, and in vivo ECG evaluation in a six-month dog study. At clinically relevant concentrations of omacetaxine, these studies predicted that drug-related QT prolongation was unlikely.

6 CLINICAL DEVELOPMENT

6.1 Clinical Trial Program

Data from 212 CML, acute myeloid leukemia (AML) and solid tumor patients in six clinical studies provide pharmacokinetic (PK), efficacy, and safety results supporting the proposed indication in the NDA (Table 3).

Table 3. Omacetaxine Clinical Development Program

Study No.	Indication	Design	Number of Patients
CML-202	CML patients who have failed imatinib and have the Bcr-Abl T315I mutation	Phase 2, open label, single-arm	66
CML-203	CML patients who have failed two or more TKIs	Phase 2, open label, single-arm	65
04.2/04.3	CML-AP who have failed imatinib	Pilot study	4
CGX-205	Solid and hematologic tumors	Phase 1, PK	21
AML-204	Relapsed or refractory AML	Simon 2-stage Phase 2	13
CML-206	Compassionate use program – CML and AML	Retrospective data collection	43
		Total	212

The pivotal study CML-202 is an ongoing efficacy and safety study of omacetaxine therapy in each of the CML disease phases (CML-CP, CML-AP and CML-BP) in patients who have failed imatinib and have the Bcr-Abl T315I mutation. Patients are treated with SC omacetaxine at 1.25 mg/m^2 twice daily for up to 14 days per 28 day cycle. Patients who demonstrate response are converted to maintenance therapy (SC omacetaxine 1.25 mg/m^2 twice daily for 7 consecutive days every 28 days). Further details on the treatment are provided in Section 6.3.1.3.

The data for study CML-202 included in the initial NDA submission were analyzed using a data cut-off date of March 6, 2009. These data were subsequently updated using a cut-off date of September 17, 2009. With the update, 54% of patients on study CML-202 have had a duration of study participation greater than 6 months, and 26% have participated on study for greater than 12 months.

Supportive evidence for the efficacy of omacetaxine in CML is provided from two additional studies: CML-203 and 04.2/04.3. Study CML-203 is an ongoing study evaluating the safety and efficacy of subcutaneously administered omacetaxine in patients with CML who have failed treatment or demonstrated intolerance to at least two prior TKI therapies. Study 04.2/04.3 was a pilot safety and efficacy study of omacetaxine in patients with CML-AP who were refractory or intolerant to imatinib therapy. The dose and dosing schedule used in these two supportive studies were identical to those used in study CML-202.

Three additional studies also support the safety evaluation of omacetaxine. In study CGX-205, pharmacokinetic (PK) data were obtained from patients with hematologic and solid tumors. This study also included dense ECG measurements to evaluate potential for QT effects. Patients were treated with SC omacetaxine using the treatment schedule from the CML studies listed above.

Study AML-204 was a pilot safety and efficacy study in patients with relapsed or refractory AML. This study was conducted in France, and treatment consisted of SC omacetaxine at 2.5 mg/m^2 twice daily for 9 consecutive days every 28 days.

Lastly, study CML-206 was a retrospective collection of data from patients who were treated with omacetaxine under the Autorisations Temporaires d'Utilisation (ATU) procedures in France. The goal of this study was to supplement the data regarding the use of omacetaxine for CML or AML with the particular aim of obtaining actual clinical practice information on the safety profile of omacetaxine.

6.2 Rationale for CML Study Dose Selection

The published literature provides support for the SC administration of omacetaxine at a dose of 1.25 mg/m^2 twice daily[41]. As the dose, schedule and route of administration were well established at the time ChemGenex began clinical studies, further exposure-response studies were not conducted.

6.3 Clinical Design and Evaluation

The efficacy of omacetaxine in CML is supported by data from three studies: CML-202, CML-203, and 04.2/04.3.

6.3.1 Study CML-202

Study CML-202 is an ongoing multicenter, international, single-arm, open-label study conducted at 33 centers in 11 countries. The presence of the T315I mutation was confirmed in all patients prior to enrollment. The purpose of the study is to evaluate the safety and efficacy of SC omacetaxine treatment in adult patients with CML-CP, CML-AP, or CML-BP who have the Bcr-Abl T315I mutation. Because there are no available proven therapies for the treatment of these patients, this study was designed as a single-arm, non-comparative study.

6.3.1.1 Disease Classification

Patients were classified into one of the three disease phases according to the standard definitions:

> **Chronic phase (CML-CP):** blasts < 15% in the peripheral blood or bone marrow, and basophils < 20% in the peripheral blood, and platelets > 100 x 10^9/L.
>
> **Accelerated phase (CML-AP):** blasts ≥ 15% and < 30% in the peripheral blood or bone marrow, or blasts + promyelocytes ≥ 30% in the peripheral blood or bone marrow (providing that blasts < 30%), or basophils ≥ 20% in the peripheral blood, or platelets < 100 x 10^9/L unrelated to therapy.
>
> **Blast phase (CML-BP):** blasts ≥ 30% in the peripheral blood or bone marrow, or extramedullary disease located outside the liver or spleen.

6.3.1.2 Definitions of Imatinib Failure

Patients entering the study must have been treated with and failed prior therapy with imatinib. As it was important that patients have received optimal opportunity to respond to imatinib treatment, the following definition was used for defining imatinib failure:

> Failed prior imatinib therapy, with either primary (never achieved a response) or secondary resistance (loss of response), following imatinib therapy of at least

400 mg/day for CML-CP or 600 mg/day for CML-AP and CML-BP, or if such doses were not tolerated, the highest dose tolerated in the patient.

Failure was defined as one of the following:

i) No CHR by 12 weeks (whether lost or never achieved)

ii) No cytogenetic response by 24 weeks (i.e., 100% Ph+) (whether lost or never achieved)

iii) No MCyR by 52 weeks (i.e., ≥ 35% Ph+) (whether lost or never achieved)

iv) Progressive leukocytosis:

  (a) Increased white blood cell count on at least two consecutive evaluations, at least 2 weeks apart and doubling from the nadir to ≥ 20 x 10^9/L or

  (b) Absolute increase in white blood cell (WBC) by ≥ 50 x 10^9/L above post-imatinib nadir

6.3.1.3 Treatment Schedule

Study treatment consisted of omacetaxine 1.25 mg/m^2 administered by SC injection twice daily for 14 consecutive days every 28 days (induction therapy). The number of days of dosing could be adjusted for toxicity, most frequently due to myelosuppression. In these cases, the practical implementation of dose reductions was achieved by investigators by reducing the number of daily doses prescribed during the next cycle by two days when patients experienced platelet levels < 50 x 10^9/L and/or absolute neutrophil count (ANC) < 0.5 x 10^9/L. No adjustments were made to the mg/m^2 dosage. The desired goal for all dose adjustments during therapy was to establish and maintain as close to a 28-day dosing cycle as possible. Patients who demonstrated response (described below) were converted to maintenance therapy (SC omacetaxine 1.25 mg/m^2 twice daily for 7 consecutive days every 28 days).

Continuation of therapy beyond 24 months was allowed following discussion between ChemGenex and the principal investigator, based on the patient response status and whether the patient was able to tolerate further treatments.

Patients were permanently removed from study for any of the following reasons:

- Failure to achieve a meaningful hematologic or cytogenetic response after six cycles

- Disease progression
- An excessive grade 3-4 toxicity without a response to treatment or other adverse event which, in the opinion of the investigator, warranted permanent withdrawal
- Treatment with a prohibited concomitant medication
- Patient noncompliance
- At the request of the patient, Principal Investigator, Sponsor, or regulatory authority
- Patient death

During the study, patients were provided with drug supplies that allowed them to administer the drug at home, either by themselves or by an assistant such as a visiting nurse. At their first clinic visit, each patient was given training on reconstitution and administration of the drug. Each treatment required that one vial of lyophilized omacetaxine be reconstituted with sterile saline, and the appropriate dose drawn up into a 1 mL syringe for SC injection.

6.3.1.4 Bcr-Abl and T315I Mutation Testing

For molecular studies, patient samples were analyzed at one of the two reference laboratories, one in the US and one in Europe. Peripheral blood samples from patients were tested for Bcr-Abl transcript levels prior to each omacetaxine treatment cycle and for Bcr-Abl kinase domain mutations on screening and prior to every third omacetaxine treatment cycle. Both reference laboratories measured the levels of the Bcr-Abl transcript by standard quantitative reverse transcription polymerase chain reaction (qRT-PCR) methods. The data obtained were expressed as a ratio (percentage) of the amount of Bcr-Abl transcript measured to the normal Abl (Abelson) fragment measured in each patient’s sample.

For detection of Bcr-Abl T315I mutations, two different techniques were utilized. In the US the Abl kinase domain was amplified and sequenced. If the T315I mutation was detected, the amount of mutated T315I Bcr-Abl transcript was quantified by rapid pyrosequencing[59, 60]. In Europe the T315I mutation was detected by denaturing high-performance liquid chromatography[61]. If the sample was found to be positive for the T315I mutation, the mutation was quantified by qRT-PCR.

6.3.1.5 Study Assessments and Endpoints

Primary efficacy assessments included the following: complete blood count performed prior to each dosing cycle and weekly during the 14 day dosing schedule, and bone marrow aspiration and cytogenetic analysis performed every three months. The endpoints used to evaluate efficacy in study CML-202 were based on standard criteria employed in the evaluation of CML, and are the same as those used previously for the review of the approved TKIs[23, 24]. Major cytogenetic response is an accepted surrogate for survival and was used as the basis of approval for imatinib, dasatinib, and nilotinib[3-5]. For CML-AP and CML-BP, hematologic responses are considered to be the primary endpoints that are predictive of clinical benefit[3-5]. The specific definitions were dependent on the patient's disease phase:

CML-CP:

- **Major cytogenetic response** (MCyR): Complete or partial cytogenetic response, up to 35% Ph+ metaphases
- **Complete hematologic response** (CHR): WBC < 10 x 10^9/L; platelets < 450 x10^9/L; myelocytes + metamyelocytes < 5% in blood; no blasts or promyelocytes in blood; < 20% basophils in peripheral blood; no extramedullary involvement

CML-AP and CML-BP:

- **MCyR**
- **Overall hematologic response:**
  - **CHR:** ANC ≥ 1.5 x 10^9/L; platelets ≥ 100 x 10^9/L; no blood blasts; bone marrow blasts < 5%; no extramedullary disease
  - **No evidence of leukemia** (NEL): morphologic leukemia-free state, defined as < 5% bone marrow blasts
  - **Return to chronic phase** (RCP): < 15% blasts bone marrow and peripheral blood; < 30% blasts + promyelocytes in bone marrow and peripheral blood; < 20% basophils in peripheral blood; no extramedullary disease other than spleen and liver

As the majority of CML-CP patients who entered study CML-202 had failed multiple TKI therapies and/or chemotherapies, durable hematologic response is also a meaningful clinical response and is predictive of clinical benefit for all disease groups.

The secondary endpoints included suppression of Bcr-Abl transcript levels, reduction in the proportion of Bcr-Abl T315I mutation from baseline, the time to onset and duration of best clinical response, and overall survival. Overall survival was defined as the time, in months, from the first dose in Cycle 1 until death from any cause. Survival time was censored using the date of last recorded contact or evaluation when the patient was alive at the time of the analysis.

6.3.1.6 Statistical Analysis Plan

Because study CML-202 was an open-label, non-randomized study, descriptive statistics were used for the majority of analyses. The study was initially designed as a Simon Two-Stage design. In 2006, the estimation of sample size was changed to use an adaptive design methodology. The adaptive design specified that the target enrollment for each disease phase would be determined by the independent data monitoring committee (DMC) after the response of a minimum of 10 patients was adjudicated. Target sample size re-estimation was to be conducted by the DMC based on the proportion of patients classified as having a clinical response, relative to an *a priori* boundary of 2.5%. The *a priori* boundary was the pre-specified value stated in the null hypothesis, relative to the lower limit of the one-sided 95% confidence limit. However, following discussions with the FDA, and given the difficulty of enrolling patients, the final target for enrollment was estimated based on an assessment of obtaining data from sufficient number of patients on which a benefit/risk assessment could be made.

6.3.1.7 Independent Data Monitoring Committee

In order to assure non-biased and objective assessments of primary efficacy endpoints, an independent DMC consisting of two board certified hematologist/oncologists was convened to review the laboratory and cytogenetic data, according to a pre-defined charter. The adjudication of response as determined by the DMC formed the basis for all efficacy results reported in this study.

6.3.2 Study CML-203

Study CML-203 is an ongoing open label, multi-center study evaluating the safety and efficacy of subcutaneously administered omacetaxine in patients with CML who have failed treatment, demonstrated intolerance, or a experienced a combination of prior failure and intolerance to at least two TKI therapies (regardless of their Bcr-Abl mutation status, with the exception of the T315I mutation). The study design was identical to that for study CML-202. The same endpoints were used in study CML-203 as in study CML-202, with the exception of one secondary endpoint which was not included in study CML-203 (reduction in the proportion of Bcr-Abl T315I mutation from baseline). This study provides important supportive efficacy information in the overall assessment of omacetaxine activity.

6.3.3 Study 04.2/04.3

Study 04.2/04.3 was a safety and efficacy study of omacetaxine in patients with CML-AP who were refractory or intolerant to imatinib therapy. This study was conducted as a pilot study in France and the UK prior to the opening of studies CML-202 and CML-203. As with studies CML-202 and CML-203, hematologic and cytogenetic response endpoints were used in this study.

7 CLINICAL PHARMACOLOGY

The clinical PK of omacetaxine was evaluated in a multiple-dose PK study of SC administered omacetaxine from patients with relapsed and/or refractory hematologic malignancies and in patients with advanced solid tumors with no bone marrow involvement (study CGX-205). A total of 21 patients were included in the PK population after receiving at least one dose of 1.25 mg/m^2 omacetaxine via SC injection. PK parameters are summarized in Table 4. Omacetaxine was rapidly absorbed into plasma following SC injection as evidenced by measureable plasma concentrations at 0.5 hours after dosing. Mean omacetaxine C_{max} values were higher on Day 11 (36.2 ng/mL) compared to Day 1 (25.1 ng/mL) implying there was some degree of accumulation as indicated by a mean accumulation index (RACC) of 1.45. The mean half-life after the first dose on Day 1 (6.96 hours) was nearly identical to that at steady state on Day 11 (7.03 hours). PK data for the omacetaxine metabolites, 4′-demethyl-homoharringtonine (4′-DMHHT) and cephalotaxine were also assessed in this study. The half-life for 4′-DMHHT was longer than for omacetaxine, averaging about 16 hours, but the overall exposure to 4′-DMHHT, based on AUCτ values, was only about 13% that of omacetaxine. The other omacetaxine metabolite measured in the study, cephalotaxine, could not be quantified in the vast majority of plasma samples, indicating that cephalotaxine is not a major metabolite.

Table 4. Summary of SC Omacetaxine Pharmacokinetic Parameters (Study CGX-205)

Study Day (n)	C_{max} (ng/mL) Mean (%CV)	T_{max} (h) Mean (Min, Max)	$t_{½}$ (h) Mean (SD)	AUC_{INF}/τ (h*ng/mL) Mean (%CV)	CL/F (L/h/m^2) Mean (%CV)	Vz/F (L/m^2) Mean (%CV)
1 (21)	25.1 (56.0)	0.55 (0.48-1.00)	6.96 (2.44)	136.2 (70.3)	13.5 (64.0)	126.8 (63.9)
11 (10)	36.2 (55.6)	0.60 (0.40-1.00)	7.03 (2.23)	188.0 (72.3)	10.5 (76.3)	66.2 (59.2)

Omacetaxine has a low to moderate binding to plasma proteins. The drug is not highly permeable through cell membranes and is subject to efflux by P-gp. Metabolism of omacetaxine by human hepatic microsomes appears to be very low, so the potential for drug-drug interactions is negligible. Both omacetaxine and its metabolite 4′-DMHHT are unlikely to be cytochrome P450 inhibitors or inducers at clinically relevant concentrations.

8 EFFICACY OF OMACETAXINE

Omacetaxine induces hematologic and cytogenetic responses in CML patients with the T315I mutation, as demonstrated by the efficacy data from study CML-202. The activity of omacetaxine in CML is further supported by the data from studies CML-203 and 04.2/04.3.

For studies CML-202 and CML-203, the data are presented below by disease phase: CML-CP, CML-AP, and CML-BP.

8.1 Study CML-202

8.1.1 Disposition and Baseline Characteristics

Data from 66 patients are reported in study CML-202 (CML-CP = 40 patients, CML-AP = 16 patients, and CML-BP = 10 patients) (Table 5). The presence of the T315I mutation was confirmed in all patients prior to enrollment. The study is ongoing for collection of long term data. Of the 66 patients, 14 patients were still ongoing in the study at data cut-off. Five CML-CP patients and one CML-AP patient have been on study for more than 24 months.

Table 5. Patient Disposition

	Patients, n (%)			
Patient Accounting	**CML-CP n = 40**	**CML-AP n = 16**	**CML-BP n = 10**	**Total n = 66**
Ongoing	13 (32.5%)	1 (6.3%)	0	14 (21.2%)
Discontinued	27 (67.5%)	15 (93.8%)	10 (100%)	52 (78.8%)
Discontinued primarily due to:				
Disease progression	9 (22.5%)	6 (37.5%)	6 (60.0%)	21 (31.8%)
Failure to achieve response	6 (15.0%)	1 (6.3%)	0	7 (10.6%)
Death	3 (7.5%)	3 (18.8%)	4 (40.0%)	10 (15.2%)
Adverse event	3 (7.5%)	3 (18.8%)	0	6 (9.1%)
Patient non-compliance	1 (2.5%)	0	0	1 (1.5%)
At request of patient, investigator, or sponsor	2 (5.0%)	2 (12.5%)	0	4 (6.1%)
Other*	3 (7.5%)	0	0	3 (4.5%)

*Allogeneic hematopoietic stem cell transplantation

The majority of patients discontinued the study due to disease progression or failure to achieve a response. Three CML-CP patients who discontinued the study due to “Other” all left the study to receive an allogeneic HSCT. Two of these patients had achieved a MCyR prior to leaving the study.

Patient demographics and baseline characteristics are summarized in Table 6.

Table 6. Patient Demographics and Baseline Characteristics

	Patients, n (%)			
Demography Category	**CML-CP n = 40**	**CML-AP n = 16**	**CML-BP n = 10**	**Total n = 66**
Age (years)				
Median	59	62	50	58
Min, Max	26, 83	30, 83	19, 61	19, 83
Gender				
Male	28 (70.0%)	11 (68.8%)	7 (70.0%)	46 (69.7%)
Female	12 (30.0%)	5 (31.2%)	3 (30.0%)	20 (30.3%)
Race				
Caucasian	34 (85.0%)	12 (75.0%)	7 (70.0%)	53 (80.3%)
Black	2 (5.0%)	3 (18.8%)	2 (20.0%)	7 (10.6%)
Asian	4 (10.0%)	1 (6.2%)	1 (10.0%)	6 (9.1%)
Median duration of CML (months)	48.9	90.5	35.7	53.9
Min, Max	13.1, 188.1	18.2, 285.6	5.2, 70.9	5.2, 285.6
Clonal evolution	10 (25.0%)	6 (37.5%)	7 (70.0%)	23 (34.8%)
Best response to imatinib				
MCyR	12 (30.0%)	2 (12.5%)	2 (20.0%)	16 (24.2%)
CHR	24 (60.0%)	6 (37.5%)	5 (50.0%)	35 (53.0%)
CHR at baseline	8 (20.0%)	NA	NA	8 (12.1%)

NA = not applicable

The median age of patients on study was 58 years. Many of the patients had been treated for CML for long periods of time; the median time from initial CML diagnosis to screening for study CML-202 for CML-CP patients was 48.9 months, for CML-AP patients 90.5 months, and for CML-BP patients 35.7 months. Clonal evolution, a chromosome abnormality that develops in addition to the Ph chromosome, is an indicator of more advanced disease.

Twenty five percent of the CML-CP patients, 37.5% of CML-AP patients and 70.0% of CML-BP patients had this abnormality present on study entry.

All patients had received prior imatinib therapy (Table 7). Patients were generally a heavily pre-treated, drug resistant population with the majority of patients having failed treatment with multiple TKIs. The prior use of IFN-α and chemotherapy were more common in CML-AP and CML-BP patients. HU use was permitted on study in patients with rapidly proliferating disease during the first two study cycles. The use of HU was permitted during the later cycles after consultation with the medical monitor. Of the 66 patients in study CML-202, 14 CML-CP, 7 CML-AP and 7 CML-BP patients received HU on study.

Table 7. Prior Leukemia Treatments

	Patients, n (%)			
Previous Treatments	**CML-CP n = 40**	**CML-AP n = 16**	**CML-BP n = 10**	**Total n = 66**
Imatinib	40 (100%)	16 (100%)	10 (100%)	66 (100%)
Dasatinib	19 (48%)	13 (81%)	8 (80%)	40 (61%)
Hydroxyurea	18 (45%)	9 (56%)	7 (70%)	34 (52%)
Nilotinib	12 (30%)	8 (50%)	2 (20%)	22 (33%)
Interferon	13 (33%)	9 (56%)	2 (20%)	24 (36%)
Cytarabine	5 (13%)	7 (44%)	4 (40%)	16 (24%)
Anthracyclines	0	3 (19%)	4 (40%)	7 (11%)
Other*	7 (18%)	2 (13%)	2 (20%)	11 (17%)

*Includes investigational agents bosutinib, MK-0457, and INNO-406.

8.1.2 Exposure to Omacetaxine

Exposure to omacetaxine is summarized in Table 8. The median duration of study participation was 8.1 months (CML-CP = 12.2 months, CML-AP = 2.6 months, and CML-BP = 1.2 months) with a median follow-up of 15.6 months (CML-CP = 18.7 months, CML-AP = 8.1 months, CML-BP = 2.2 months).

The median total number of cycles in which patients were treated was 5.0 (CML-CP = 7.0, CML-AP = 3.0 and CML-BP = 1.5) and median total months of exposure was 6.5 months (CML-CP = 10.0 months, CML-AP = 1.9 months, and CML-BP = 0.8 months).

Table 8. Summary of Exposure to Omacetaxine by Disease Phase

Exposure Category		CML-CP n = 40	CML-AP n = 16	CML-BP n = 10	Total n = 66
Duration of study participation (months)	Median	12.2	2.6	1.2	8.1
	95% CI	9.1-20.8	1.8-7.0	0.7-2.4	4.7-11.8
Total follow-up (months)	Median	18.7	8.1	2.2	15.6
	95% CI	15.6-25.4	3.1-19.6	1.2-9.1	11.0-18.8
Total number of cycles	Mean (SD)	9.6 (7.4)	5.4 (7.1)	2.3 (2.0)	7.5 (7.3)
	Median	7.0	3.0	1.5	5.0
	Min, Max	1.0-31.0	1.0-29.0	1.0-7.0	1.0-31.0
Total months of exposure	Mean (SD)	11.4 (8.2)	5.2 (7.5)	2.0 (2.6)	8.5 (8.3)
	Median	10.0	1.9	0.8	6.5
	Min, Max	0.5-34.1	0.5-27.7	0.1-7.3	1.0-34.1

8.1.3 Response Data

The DMC adjudicated the response for each patient using all available hematology and cytogenetic data at the time of data cut-off. Shown in Table 9 are the response rates for patients in each of the three disease phases: CML-CP, CML-AP, and CML-BP.

Table 9. Study CML-202: Cytogenetic and Hematologic Response Rates

Response Category	CML-CP n = 40	CML-AP n = 16	CML-BP n = 10
	Patients, n (%)		
Cytogenetic			
MCyR	10 (25.0%)	1 (6.3%)	0
One sided 95% CI	12.7%	0.2%	0
CCyR	6 (15.0%)	1 (6.3%)	0
PCyR	4 (10.0%)	0	0
Hematologic			
Overall HR	34 (85.0%)	6 (37.5%)	3 (30.0%)
One-sided 95% CI	70.2%	15.2%	6.7%
CHR	34 (85.0%)	5 (31.3%)	2 (20.0%)
RCP	NA	1 (6.3%)	1 (10.0%)

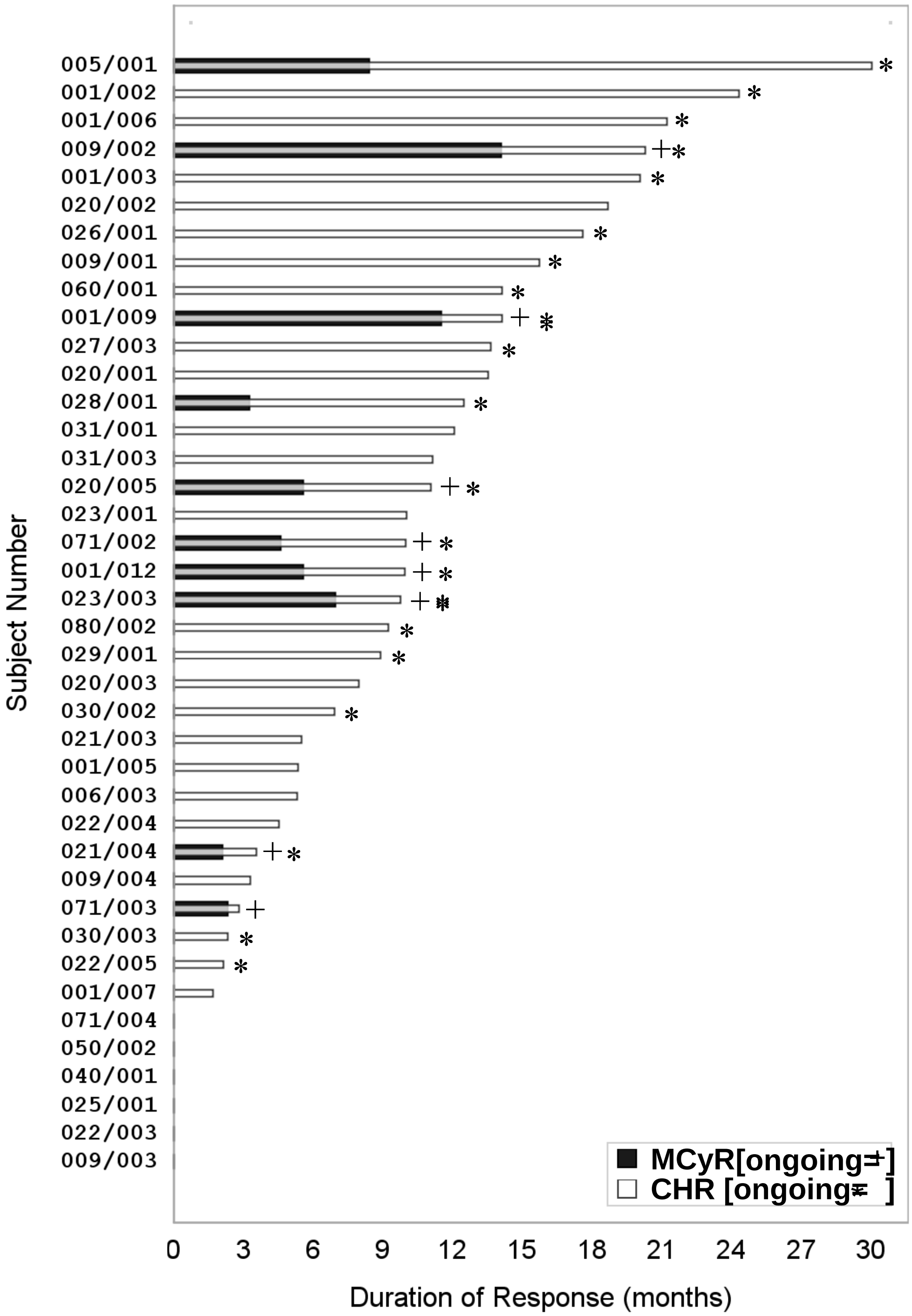
MCyR = major cytogenetic response; CCyR = complete cytogenetic response; PCyR = partial cytogenetic response; HR = hematologic response; CHR = complete hematologic response; RCP = return to chronic phase

The efficacy results for each group of patients, CML-CP, CML-AP, and CML-BP, are described further below.

<u>Chronic phase patients</u>

A MCyR was achieved by ten CML-CP patients (25.0%, one-sided 95% lower CI, 12.7%) with six achieving a CCyR and four achieving a PCyR (Table 9; Figure 1). A summary of the ten patients who achieved MCyR is provided in Section 8.1.4 of this document. An additional six CML-CP patients (15.0%) achieved minimal cytogenetic response (> 65% to 95% Ph+ cells).

Figure 1. Graphical Display of CHR and MCyR Responses in CML-CP patients

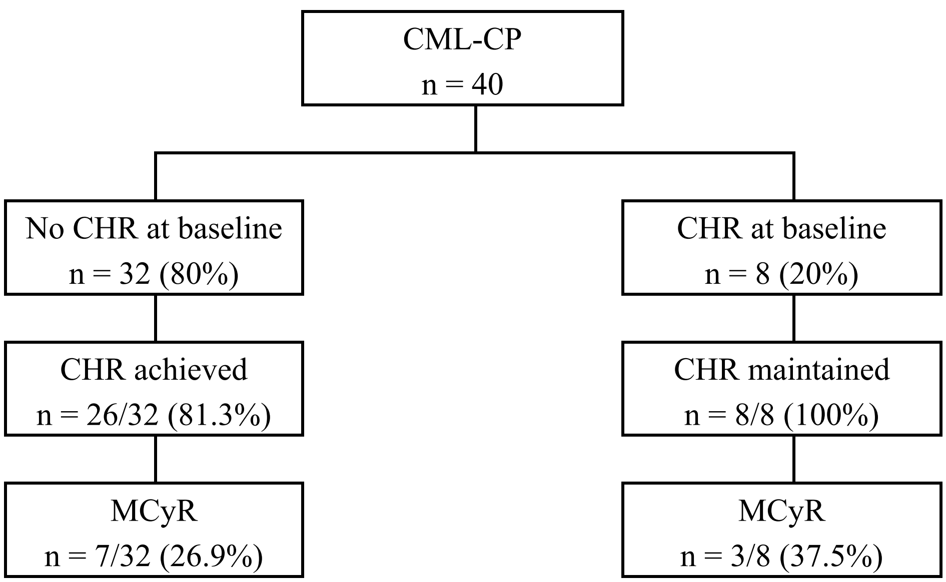


Patients 023/003, 021/004 and 022/003 discontinued the study to receive a HSCT.

Patients who achieved a MCyR did so within 1.7 to 7.8 months of treatment (median 4.9 months). The median duration of MCyR could not be estimated; however, the response was ongoing in 8 of the 10 patients at the time of data cut-off or discontinuation from study (Figure 1). Two patients discontinued the study to received an HSCT.

An overall hematologic response (CHR) was achieved by 34 of 40 patients (85.0%) with a median duration of 18.7 months (95% CI, 11.1, NA). Eight of these 34 patients entered the study in CHR and maintained their response for > 8 weeks to be considered responders (Figure 2). The median time to onset of CHR was 0.4 months. Of the 32 patients who entered the study without CHR, 20 patients had received substantial treatment with HU at baseline suggesting that some CML patients are refractory to HU treatment when the T315I mutation is present.

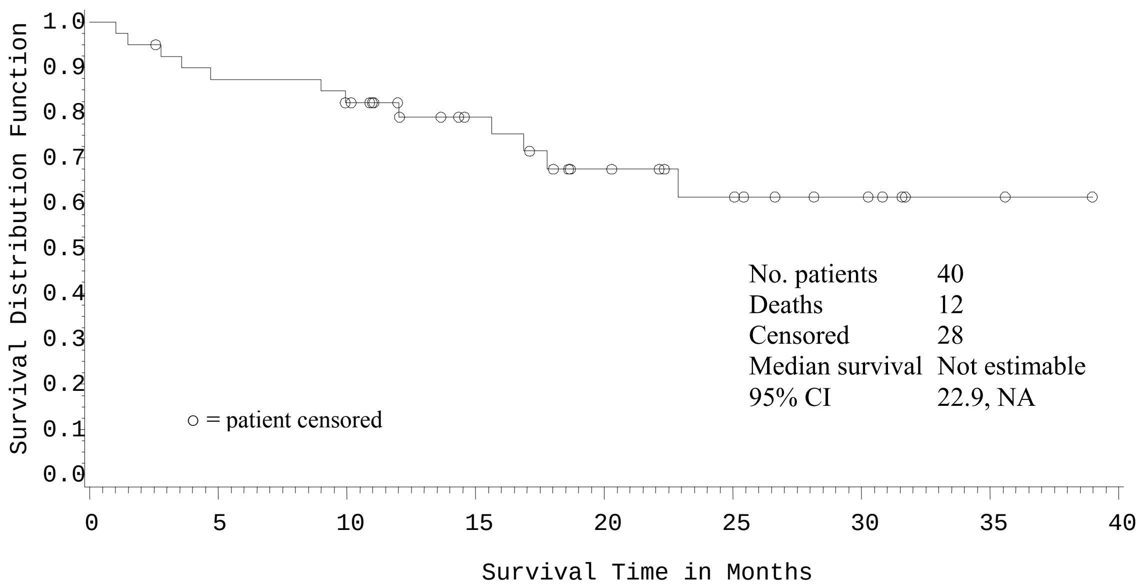
Figure 2. Effect of Baseline CHR Status on Hematologic and Cytogenetic Responses in CML-CP Patients in Study CML-202



For CML-CP patients, a median overall survival could not be estimated at the time of data cut-off because greater than 50% of the patients were still alive. Long-term survival data was collected via a telephone based survey (data cut-off December 2009). At that time, 12 of

40 patients (30.0%) were reported as having died and the probability of survival was over 50% for the entire observation period (Figure 3).

Figure 3. Kaplan-Meier Estimate of Overall Survival in T315I CML-CP Patients from Entry into Study CML-202



Note: Patients who discontinued the study and were alive at the time of study discontinuation were censored at their last recorded contact date. Ongoing patients who were alive at the time of analysis were censored at the data cut-off date (December 2009).

Of the six CML-CP patients who achieved a CCyR, three patients achieved a major molecular response, defined as a ratio of Bcr-Abl/Abl of less than 0.1% according to the international scale.

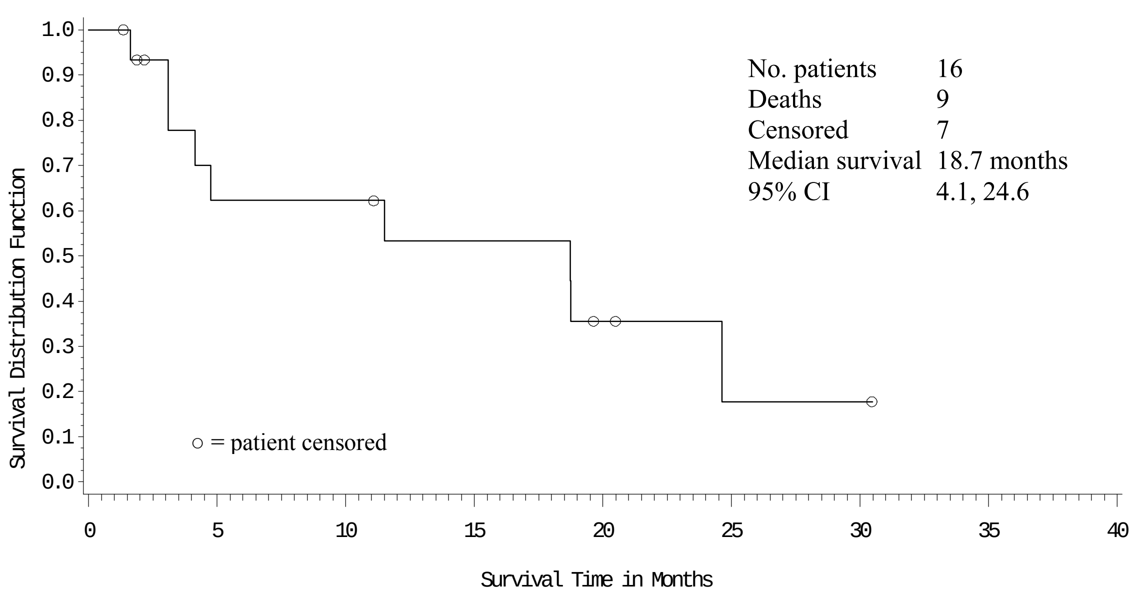
Of the 30 CML-CP patients with at least one post-baseline assessment of their T315I mutation, reduction in the mutant clone was noted in 17 patients: two patients (6.7%) had a 100% reduction, five patients (16.7%) had a 50 to 74% reduction, seven patients (23.3%) had a 25 to 49% reduction, and three patients (10%) had a 1 to 24% reduction.

Accelerated phase patients

An overall hematologic response (i.e., CHR, RCP, or NEL) was achieved by six of the 16 CML-AP patients (37.5%, Table 9). The median time to onset could not be statistically estimated, but five out of the six patients achieved a response after less than 1 month on study. All six responses were achieved by the end of Cycle 1. The median duration of hematologic response was 14.8 months (95% CI, 3.7, 14.8). One patient achieved a CCyR after 2.8 months on study and the duration of response was 8.3 months; the response is ongoing. This patient also achieved a major molecular response.

The median overall survival for CML-AP patients was 18.7 months (95% CI 4.1, 24.6) (Figure 4).

Figure 4. Kaplan-Meier Estimate of Overall Survival in T315I CML-AP Patients from Entry into Study CML-202



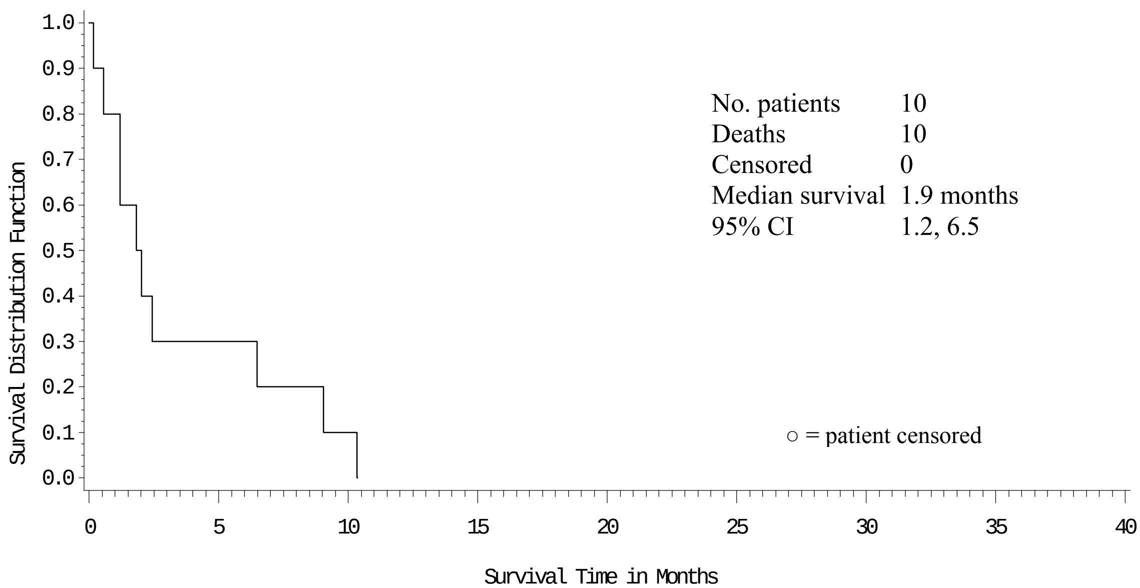
Note: Patients who discontinued the study and were alive at the time of study discontinuation were censored at their last recorded contact date. Ongoing patients who were alive at the time of analysis were censored at the data cut-off date (December 2009).

Blast phase patients

Three of 10 CML-BP patients (30%) achieved an overall hematologic response (i.e., CHR, RCP, or NEL) (Table 9). All three patients who achieved this response did so by the end of Cycle 1. The median time to onset of hematologic response in CML-BP patients could not be estimated. The median duration of response was 3.3 months (95% CI 2.2, 4.4).

The median overall survival was 1.9 months (95% CI 1.2, 6.5) (Figure 5).

Figure 5. Kaplan-Meier Estimate of Overall Survival in T315I CML-BP Patients from Entry into Study CML-202



Note: Patients who discontinued the study and were alive at the time of study discontinuation were censored at their last recorded contact date. Ongoing patients who were alive at the time of analysis were censored at the data cut-off date (December 2009).

8.1.4 Patient Narratives for Patients Achieving MCyR

The following summaries for the ten CML-CP patients and one CML-AP patient who achieved MCyR provide evidence of the clinical benefit that was achieved by these heavily pre-treated and refractory patients.

- CML-CP patient 001/009 achieved a CHR 8 days after the first dose of study drug and achieved a confirmed CCyR 2.8 months after the first dose of study drug. The duration of CHR was 14.1 months, and the duration of the confirmed CCyR was 11.5 months; both responses were ongoing at the time of data cut-off. The patient had received prior therapy with imatinib, dasatinib, and SKI-606 (bosutinib). The patient was not receiving hydroxyurea at the start of the study.

- CML-CP patient 001/012 entered the study with CHR and achieved a confirmed PCyR 4.3 months after the first dose of study drug. The patient's CHR lasted for 9.9 months, and the duration of the confirmed PCyR was 5.6 months. Both responses were ongoing at the time of data cut-off. The patient had received prior therapy with imatinib.

- CML-CP patient 005/001 achieved a CHR 8 days after the first dose of study drug and achieved a confirmed CCyR 7.8 months after the first dose of study drug. The duration of CHR was 30.3 months and was ongoing at the time of data cut-off. The duration of the confirmed CCyR was 8.4 months. The patient lost the best cytogenetic response, a CCyR, but maintained a MCyR for an additional 13 months with the response ongoing at the time of data cut-off. The patient had received prior therapy with imatinib, nilotinib, cytarabine, interferon, and hydroxyurea. The patient was not receiving hydroxyurea at the start of the study.

- CML-CP patient 009/002 entered the study with CHR and achieved a confirmed CCyR 6.2 months after the first dose of study drug. The duration of CHR was 20.3 months, and the duration of the confirmed CCyR was 14.1 months; both responses were ongoing at the time of data cut-off. The patient had received prior therapy with imatinib, dasatinib, and interferon. The patient was not receiving hydroxyurea at the start of the study.

- CML-CP patient 020/005 entered the study with CHR and achieved an unconfirmed CCyR 5.5 months after the first dose of study drug. The patient's CHR lasted for 11.1 months, and the duration of the unconfirmed CCyR was 5.6 months. Both responses were ongoing at the time of data cut-off. The patient had received prior therapy with imatinib, dasatinib, and hydroxyurea.

- CML-CP patient 021/004 achieved CHR 8 days after the first dose of study drug and achieved an unconfirmed PCyR 1.7 months after the first dose of study drug. The duration of CHR was 3.6 months, and the duration of the unconfirmed PCyR was 2.1 months; both responses were ongoing at the time of data cut-off. Confirmation of this response was not possible as the patient became eligible for an allogeneic hematopoietic stem cell transplantation and discontinued from study. The patient had received prior therapy with imatinib, dasatinib, and hydroxyurea. The patient was receiving 1 g/day of hydroxyurea for 52 days preceding the start of the study.

- CML-CP patient 023/003 achieved CHR 7 days after the first dose of study drug and achieved a confirmed CCyR 3.0 months after the first dose of study drug. The duration of CHR was 9.7 months, and the duration of the confirmed CCyR was 6.9 months; both responses were ongoing at the time of study discontinuation when the patient became eligible to receive a cord blood transplantation. The patient had received prior therapy with imatinib. The patient had received a 16-day course of hydroxyurea (500 mg/day) that ended 4 days prior to the start of the study.

- CML-CP patient 028/001 achieved CHR 8 days after the first dose of study drug and achieved an unconfirmed PCyR 2.1 months after the first dose of study drug. The duration of CHR was 12.5 months, and the response was ongoing at the time of data cut-off. The duration of the unconfirmed PCyR was 3.3 months. The patient had received prior therapy with imatinib. The patient received a 42-day course of hydroxyurea (1 g/day) that ended 4 days prior to the start of the study.

- CML-CP patient 071/002 achieved CHR 7 days after the first dose of study drug and achieved a confirmed PCyR 5.6 months after the first dose of study drug. The patient's CHR lasted for 10.0 months, and the duration of the confirmed PCyR was 4.6 months. Both responses were ongoing at the time of data cut-off. The patient had received prior therapy with interferon, imatinib, dasatinib, and hydroxyurea.

- CML-CP patient 071/003 achieved CHR 14 days after the first dose of study drug and achieved an unconfirmed CCyR 6.6 months after the first dose of study drug. The patient's CHR lasted for 2.8 months, and the duration of the unconfirmed CCyR was 2.3 months and was ongoing at the time of data cut-off. The patient had received prior therapy with imatinib and hydroxyurea.

- CML-AP patient 080/001 achieved CHR 57 days after the first dose of study drug and achieved a confirmed CCyR 9.2 months after the first dose of study drug. The duration of CHR was 2.8 months, and the duration of the confirmed CCyR was 8.3 months; both responses were ongoing at the time of data cut-off. The patient had received prior therapy with imatinib, interferon, daunorubicin, cytarabine, and etoposide. The patient received a 6-day course of hydroxyurea (500 mg/day) that ended 8 days prior to the start of the study

8.2 Study CML-203

Patients with CML who are resistant or intolerant to two or more TKIs were enrolled in study CML-203. The data from this study provide supportive evidence for the efficacy of omacetaxine in CML. Enrolment in this study was initiated approximately 12 months after the start of study CML-202, and therefore patient follow-up is of a shorter duration.

Descriptive statistics were used to summarize the efficacy data available as of the data cut-off date (March 6, 2009) (Table 10).

Table 10. Study CML-203: Cytogenetic and Hematologic Response Rates

Response Category	CML-CP n = 30	CML-AP n = 20	CML-BP n = 15
	Patients, n (%)		
Cytogenetic			
MCyR	6 (20.0)	1 (5.0)	0
CCyR	1 (3.3)	1 (5.0)	0
PCyR	5 (16.7)	0	0
Hematologic			
Overall HR	24 (80.0)	15 (75.0)	8 (53.3)
CHR	24 (80.0)	12 (60.0)	6 (40.0)
RCP	NA	3 (15.0)	2 (13.3)

Of the 30 patients in CML-CP, six (20%) achieved a MCyR; time to cytogenetic response ranged from 3 to 6 month after first dose. The median duration of MCyR could not be statistically estimated; however, the response was ongoing in 5 of the 6 patients at the time of data cut-off or study discontinuation. One CML-AP patient achieved a PCyR. A summary of the patients achieving MCyR is provided in the next section.

The hematologic response rates in study CML-203 differed slightly from those in study CML-202 by disease phase, with higher rates of response in CML-AP and CML-BP patients.

8.2.1 Patient Narratives for Patients Achieving MCyR in Study CML-203

The following summaries for the six CML-CP patients and one CML-AP patient who achieved MCyR in study CML-203 provide evidence of the clinical benefit that was achieved by these patients.

- CML-CP patient 310/001 entered the study with CHR and achieved an unconfirmed PCyR 2.8 months after the first dose of study drug. The duration of CHR was 4.6 months, and the duration of the unconfirmed PCyR was 1.8 months. The patient received an allogeneic HSCT after achieving a PCyR; both the hematologic and cytogenetic responses were ongoing at the time of study discontinuation. The patient had received prior therapy with imatinib and dasatinib. The patient was not receiving hydroxyurea at the start of the study.

- CML-CP patient 311/002 entered the study with CHR and achieved a confirmed PCyR 2 months after the first dose of study drug. The duration of CHR was 4 months, and the duration of the confirmed PCyR was 1.9 months; both responses were ongoing at the time of data cut-off. This patient discontinued the study 12 days after the data cut-off in order to receive an allogeneic HSCT. The patient had received prior therapy with imatinib, dasatinib, and SKI-606 (bosutinib). The patient was not receiving hydroxyurea at the start of the study.

- CML-CP patient 320/002 achieved CHR 34 days after the first dose of study drug and achieved a confirmed PCyR 5.7 months after the first dose of study drug. The duration of CHR was 7.5 months, and the duration of the confirmed PCyR was 2.9 months; both responses were ongoing at the time of data cut-off. The patient had received prior therapy with imatinib, dasatinib, nilotinib, cytarabine, and interferon. The patient was receiving 1 g/day of hydroxyurea for 13 days preceding the start of the study.

- CML-CP patient 323/001 achieved CHR 26 days after the first dose of study drug and achieved an unconfirmed PCyR 3.7 months after the first dose of study drug. The duration of CHR was 7.5 months, and the duration of the unconfirmed PCyR was 0.9 months. The patient discontinued the study after 4.6 months; the reason for discontinuation was recorded as “request of the patient, investigator or sponsor”. Both responses were ongoing at the time of study discontinuation. The patient had received prior therapy with imatinib, dasatinib, and busulfan. The patient was not receiving hydroxyurea at the start of the study.

- CML-CP patient 324/002 entered the study with CHR and achieved an unconfirmed CCyR 5.4 months after the first dose of study drug. The duration of CHR was 4.7 months, and the duration of the confirmed CCyR was 2.6 months; both responses were ongoing at the time of data cut-off. The patient had received prior therapy with imatinib, dasatinib, nilotinib, cytarabine, etoposide, idarubicin, interferon, and hydroxyurea. The patient was not receiving hydroxyurea at the start of the study.

- CML-CP patient 327/001 achieved CHR 16 days after the first dose of study drug and achieved an unconfirmed PCyR 5.4 months after the first dose of study drug. The duration of CHR was 6 months, and the duration of the unconfirmed PCyR was 1.4 months. The patient had received prior therapy with imatinib, dasatinib, nilotinib, hydroxyurea, interferon, and YNK01. The patient was not receiving hydroxyurea at the start of the study.

- CML-AP patient 301/001 achieved CHR 4 days after the first dose of study drug and achieved an unconfirmed PCyR 3.5 months after the first dose of study drug. The duration of CHR was 3.5 months, and the duration of the unconfirmed PCyR was 2 days. The patient discontinued the study after 3.6 months in order to receive a stem cell transplant; both the hematologic and cytogenetic responses were ongoing at the time of study discontinuation. The patient had received prior therapy with imatinib, hydroxyurea, and SKI-606 (bosutinib). The patient was receiving 0.5 g/day of hydroxyurea for 3 days prior to the start of the study.

8.3 Study 04.2/04.3

Four patients were enrolled in this study. Two patients harbored the T315I mutation, and both patients achieved hematologic responses (CHR or RCP) and cytogenetic responses (one minimal, < 35-65% Ph+ cells; one minor, < 65-95% Ph+ cells).

8.4 Efficacy Conclusions

The CML T315I patient has no effective treatment options and there is an immediate need for a proven therapy. Left untreated, these patients will experience disease progression and shortened life expectancy. Treatment of the CML T315I patients with omacetaxine has proven effective. In study CML-202, CML-CP patients treated with omacetaxine achieved durable hematologic and cytogenetic responses with a rapid onset, and advanced disease phase patients (CML-AP and CML-BP) achieved high rates of CHR. Two of the three patients who left the study to receive an allogeneic HSCT had achieved a MCyR during omacetaxine therapy. Treatment with omacetaxine also induced major molecular responses in patients who had achieved a CCyR. The overall survival data from study CML-202 exceeds that from the literature[37]. Response data from study CML-203 are similar to the study CML-202 data and provide support for the efficacy claim of omacetaxine.

9 SAFETY OF OMACETAXINE

The full safety database evaluating SC omacetaxine comprises data from 212 patients enrolled across the six studies outlined in Table 3 ('full safety database'). The safety evaluation detailed in this briefing document provides data on this overall safety database, as well as on a subset of data from the 131 patients enrolled in the pivotal study and supportive CML study (studies CML-202 and CML-203) ('CML safety cohort'). The severity of adverse events occurring on study was graded by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Overall, the major safety concern identified was myelosuppression. Myelosuppression is a recognized complication of CML therapy and an anticipated adverse event in these heavily pre-treated patients. The myelosuppression was predictable and managed by adjusting the number of dosing days per cycle. Non-hematologic toxicities were generally mild to moderate in severity and typically not dose limiting.

9.1 Common Adverse Events

Of the 212 patients in the full safety database, 206 (97.2%) reported at least one treatment-emergent adverse event (TEAE) (Table 11). The most commonly reported adverse events were related to hematologic toxicity, with 50.9% thrombocytopenia, 43.9% anemia and 30.7% neutropenia. The most frequent non-hematologic TEAEs were diarrhea (39.6%), nausea (28.3%), fatigue (26.9%), pyrexia (26.4%), and asthenia (19.8%).

The findings of the full safety database are similar to those of the CML safety cohort. Of the 131 patients in the CML safety cohort, 129 (98.5%) reported at least one TEAE. Consistent with the full safety database, the most frequently reported adverse events were hematologic toxicities and included thrombocytopenia (60.3%), anemia (48.9%), and neutropenia (38.2%). Non-hematologic TEAEs included diarrhea (42.7%), fatigue (31.3%), pyrexia (29.8%), nausea (27.5%), asthenia (21.4%), and headache (19.1%). In the CML safety cohort, the most common Grade 3 or higher events were thrombocytopenia (55.0%), neutropenia (35.1%), anemia (34.4%), leukopenia (12.2%), and febrile neutropenia (12.2%).

Table 11. Common Adverse Reactions Reported in Patients in the Full Safety Database and CML Safety Cohort, Regardless of Relationship to Study Drug

	Full Safety Database n = 212		CML Safety Cohort n = 131	
Preferred Term	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of patients with at least one adverse event	206 (97.2%)	184 (86.7%)	129 (98.5%)	116 (88.5%)
Thrombocytopenia	108 (50.9%)	95 (44.8%)	79 (60.3%)	72 (55.0%)
Anemia	93 (43.9%)	55 (25.9%)	64 (48.9%)	45 (34.4%)
Diarrhea	84 (39.6%)	10 (4.7%)	56 (42.7%)	7 (5.3%)
Neutropenia	65 (30.7%)	58 (27.4%)	50 (38.2%)	46 (35.1%)
Nausea	60 (28.3%)	5 (2.4%)	36 (27.5%)	2 (1.5%)
Fatigue	57 (26.9%)	12 (5.7%)	41 (31.3%)	9 (6.9%)
Pyrexia	56 (26.4%)	9 (4.2%)	39 (29.8%)	3 (2.3%)
Asthenia	42 (19.8%)	4 (1.9%)	28 (21.4%)	2 (1.5%)
Leukopenia	34 (16.0%)	27 (12.7%)	18 (13.7%)	16 (12.2%)
Vomiting	33 (15.6%)	3 (1.4%)	17 (13.0%)	12 (9.2%)
Headache	32 (15.1%)	5 (2.4%)	25 (19.1%)	2 (1.5%)
Cough	28 (13.2%)	2 (0.9%)	22 (16.8%)	1 (0.8%)
Injection site erythema	27 (12.7%)	0	21 (16.0%)	0
Anorexia	27 (12.7%)	2 (0.9%)	19 (14.5%)	2 (1.5%)
Arthalgia	27 (12.7%)	3 (1.4%)	22 (16.8%)	1 (0.8%)
Constipation	27 (12.7%)	7 (3.3%)	20 (15.3%)	0
Epistaxis	24 (11.3%)	1 (0.5%)	19 (14.5%)	1 (0.8%)
Edema peripheral	23 (10.8%)	2 (0.9%)	21 (16.0%)	1 (0.8%)
Febrile neutropenia	22 (10.4%)	20 (9.4%)	18 (13.7%)	16 (12.2%)
Pain in extremity	22 (10.4%)	4 (1.9%)	18 (13.7%)	3 (2.3%)
Abdominal pain	21 (9.9%)	1 (0.5%)	15 (11.5%)	0
Disease progression	18 (8.5%)	15 (7.1%)	16 (12.2%)	13 (9.9%)
Alopecia	16 (7.5%)	0	14 (10.7%)	0
Lymphopenia	15 (7.1%)	14 (6.6%)	15 (11.5%)	14 (10.7%)

Full Safety Database = Combined safety dataset of 212 patients from six studies

CML Safety Cohort = Combined safety dataset of 131 patients from studies CML-202 and CML-203

As the rate of occurrence of adverse events is similar between the full safety database (n = 212) and the CML safety cohort (n = 131), the discussion of the safety of omacetaxine in the remainder of this document will focus on the CML safety cohort (studies CML-202 and CML-203). Presentation of the data in the CML safety cohort provides relevant information on the use of omacetaxine in a population comparable to the patient population in the proposed product label. This analysis also allows for a presentation and discussion of the safety events by CML disease phase (CML-CP, CML-AP, and CML–BP).

Table 12 provides a summary of adverse events that occurred in ≥ 5% of patients in studies CML-202 and CML-203, regardless of relationship to study drug. Events are shown by disease phase.

Table 12. Adverse Reactions Reported in ≥ 5% of Patients in CML Safety Cohort (Studies CML-202 and CML-203), Regardless of Relationship to Study Drug

Preferred Term	CML-CP n = 70		CML-AP n = 36		CML-BP n= 25		Total n = 131	
	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)
Thrombocytopenia	74.3	65.7	50.0	47.2	36.0	36.0	60.3	55.0
Anemia	64.3	44.3	38.9	27.8	20.0	16.0	48.9	34.4
Diarrhea	42.9	1.4	41.7	11.1	44.0	8.0	42.7	5.3
Neutropenia	52.9	50.0	16.7	13.9	28.0	24.0	38.2	35.1
Fatigue	28.6	4.3	36.1	11.1	32.0	8.0	31.3	6.9
Pyrexia	27.1	2.9	27.8	-	40.0	4.0	29.8	2.3
Nausea	28.6	1.4	27.8	2.8	24.0	-	27.5	1.5
Asthenia	24.3	1.4	22.2	2.8	12.0	-	21.4	1.5
Headache	20.0	-	16.7	2.8	20.0	4.0	19.1	1.5
Arthralgia	20.0	1.4	11.1	-	16.0	-	16.8	0.8
Cough	12.9	1.4	19.4	-	24.0	-	16.8	0.8
Injection site erythema	22.9	-	11.1	-	4.0	-	16.0	-
Edema peripheral	12.9	-	16.7	-	24.0	4.0	16.0	0.8
Constipation	14.3	-	8.3	-	28.0	-	15.3	-
Epistaxis	15.7	-	11.1	2.8	16.0	-	14.5	0.8
Anorexia	10.0	-	19.4	2.8	20.0	4.0	14.5	1.5
Febrile neutropenia	8.6	8.6	16.7	13.9	24.0	20.0	13.7	12.2
Leukopenia	21.4	20.0	8.3	5.6	-	-	13.7	12.2
Pain in extremity	14.3	-	13.9	2.8	12.0	8.0	13.7	2.3

continued

Preferred Term	CML-CP n = 70		CML-AP n = 36		CML-BP n= 25		Total n = 131	
	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)
Vomiting	11.4	-	11.1	-	20.0	-	13.0	-
Disease progression	5.7	4.3	5.6	5.6	40.0	32.0	12.2	9.9
Lymphopenia	21.4	20.0	-	-	-	-	11.5	10.7
Abdominal pain	8.6	-	16.7	-	12.0	-	11.5	-
Alopecia	14.3	NA	5.6	NA	8.0	NA	10.7	NA
Rash	10.0	-	8.3	-	12.0	-	9.9	-
Bone pain	7.1	1.4	11.1	2.8	16.0	4.0	9.9	2.3
Chills	2.9	-	16.7	-	16.0	-	9.2	-
Back pain	12.9	2.9	8.3	-	-	-	9.2	1.5
Dyspnea	4.3	-	13.9	2.8	16.0	8.0	9.2	2.3
Leukocytosis	2.9	1.4	11.1	5.6	20.0	4.0	8.4	3.1
Hyperuricemia	5.7	-	8.3	2.8	16.0	4.0	8.4	1.5
Dizziness	8.6	-	8.3	-	8.0	-	8.4	-
Insomnia	11.4	-	-	-	12.0	-	8.4	-
Abdominal pain upper	14.3	-	2.8	-	-	-	8.4	-
Tachycardia	8.6	1.4	2.8	-	16.0	4.0	8.4	1.5
Bone marrow failure	14.3	14.3	-	-	-	-	7.6	7.6
Contusion	8.6	-	-	-	12.0	-	6.9	-
Myalgia	11.4	1.4	2.8	2.8	-	-	6.9	1.5
Pruritus	10.0	-	5.6	-	-	-	6.9	-
Mucosal inflammation	4.3	-	5.6	2.8	16.0	8.0	6.9	2.3
Upper respiratory tract infection	10.0	-	5.6	-	-	-	6.9	-
Dry skin	7.1	-	5.6	-	4.0	-	6.1	-
Erythema	8.6	-	5.6	-	-	-	6.1	-
Hypertension	8.6	-	2.8	-	4.0	4.0	6.1	0.8
Stomatitis	5.7	2.9	5.6	-	8.0	4.0	6.1	2.3
Chest pain	7.1	-	-	-	12.0	-	6.1	-
Decreased appetite	5.7	-	5.6	-	8.0	-	6.1	-
Pancytopenia	4.3	4.3	8.3	8.3	4.0	4.0	5.3	5.3
Hyperglycemia	8.6	-	-	-	4.0	4.0	5.3	0.8
Hypokalemia	1.4	-	5.6	-	16.0	-	5.3	-
Pharyngolaryngeal pain	4.3	-	2.8	-	12.0	4.0	5.3	0.8

9.2 Study Discontinuation Due to Adverse Events

Of the 131 patients in the CML safety cohort, ten patients discontinued study due to adverse event (Table 13). As expected for this patient group, the most common adverse events leading to study discontinuation were related to myelosuppression. Eight out of 10 adverse events were considered drug-related. Two events, chronic renal failure/leukocytosis and pulmonary hemorrhage were not considered to be related to drug.

Table 13. Study Discontinuations Due to Adverse Events in Studies CML-202 and CML-203

Disease Phase	Patient Number	Adverse Event
CML-CP	022-005	Aplasia
	029-001	Sepsis/febrile neutropenia/cellulitis
	071-003	Thrombocytopenia
	311-001	Diplopia/tremor
	360-001	Pancytopenia
CML-AP	001-008	Thrombocytopenia/bone marrow failure
	006-001	Leukocytosis/chronic renal failure
	007-001	Pyrexia
	370-003	Thrombocytopenia
CML-BP	301-008	Pulmonary hemorrhage

9.3 Adverse Events of Interest and Serious Adverse Events

The safety of omacetaxine is primarily characterized by the occurrence of myelosuppression. In addition to myelosuppression, three other important areas of safety were evaluated with regard to their occurrence in patients treated with omacetaxine – bleeding events, including those related to myelosuppression, cardiovascular events, and injection site reactions.

9.3.1 Myelosuppression

Myelosuppression predominantly occurred as thrombocytopenia and neutropenia and was reported more frequently in CML-CP patients compared with advanced disease CML-AP and CML-BP patients (Table 14). In the CML safety cohort, hematologic toxicity occurred in 75% of patients. Nadir values (ANC $< 0.5 \times 10^9$/L, hemoglobin < 80 g/L, and platelet count $< 10.0 \times 10^9$/L) were typically reached within 2 to 3 weeks after the first omacetaxine dose administered in each cycle, and recovery of these blood counts generally occurred within 1 to 3 weeks of the nadir. Hematologic toxicity was frequently managed by decreasing the number of dosing days per 28-day cycle. Despite the high incidence of hematologic toxicity, febrile neutropenia occurred in only 13.7% of patients. Other sequealae related to underlying myelosuppression, such as sepsis, were uncommon (≤ 5%).

Table 14. CTC Grade 3/4 Laboratory Abnormalities in the CML Safety Cohort (Studies CML-202 and CML-203)

	CML-CP n = 70 %	CML-AP n = 36 %	CML-BP n= 25 %	Total n = 131 %
Hematology parameter				
Thrombocytopenia	65.7	47.2	36.0	55.0
Neutropenia	50.0	13.9	24.0	35.1
Anemia	44.3	27.8	16.0	34.4
Leukopenia	20.0	5.6	0	12.2
Lymphopenia	20.0	0	0	10.7

9.3.2 Bleeding

Although bleeding-related events are known complications of leukemia and its treatment, serious adverse event reports of bleeding-related events occurred in only 8 (6.1%) of patients in the CML safety cohort. These included two reports each of cerebral hemorrhage, subdural hematoma, gastrointestinal hemorrhage, and pulmonary hemorrhage. Five of the eight patients had advanced disease. Six events occurred in the presence of thrombocytopenia secondary to active or progressive disease. A Grade 2 subdural hematoma (CML-BP patient) and Grade 3 gastrointestinal hemorrhage (CML-CP patient) occurred in the presence of thrombocytopenia that was likely drug-induced.

9.3.3 Cardiovascular Safety

Of the 131 patients in the CML safety cohort, a total of 26 patients (19.8%) of patients reported cardiac adverse events. A detailed analysis of the all cardiac safety data from the CML safety cohort by an independent cardiologist did not revealed a concern regarding cardiac toxicity with the SC administration of omacetaxine. Tachycardia was the most frequent cardiac event reported occurring in 11 (8.4%) of patients, of which two events were drug-related, one Grade 1 and one Grade 4. Dosing was not interrupted because of these events. Palpitations were reported in 6 (4.6%) of patients. One Grade 1 event was reported as drug-related, and dosing was not interrupted because of this event. In the CML safety cohort, two patients had reported adverse events of QTc prolongation; both were Grade 1.

A separate clinical pharmacology study CGX-205 included a thorough evaluation for the potential for QT interval prolongation. In this study, serial 12 lead electrocardiogram (ECG) measurements were obtained at specified time points during the first cycle of treatment, and ECG tracings were reviewed centrally by an independent cardiologist. The mean changes in both QTcB and QTcF measurements beyond Day 1 were consistently negative. QTc values of > 470 msec were measured in two patients. Neither of these events was recorded as an adverse event and both events rapidly resolved without drug interruption. No QTc of > 500 msec were reported.

Overall, the data does not show that omacetaxine has an effect on the QT interval, and therefore the product can be administered without a requirement for specialized cardiac monitoring.

9.3.4 Injection Site Reactions

As omacetaxine is administered by SC injection, the occurrence of injection site reactions was carefully evaluated. Of the 131 patients in the CML safety cohort, a total of 43 patients (32.8%) reported at least one injection site reaction. The majority of events were injections site erythema with a small number of reports of injection site reaction, pain, induration, bruising, pruritus, rash and inflammation. Most events were mild. In general, injection sites reactions did not impact the omacetaxine treatment schedule, or require clinical management.

9.3.5 Serious Adverse Events (SAEs)

SAEs that occurred during the study and up to 30 days after discontinuation of study drug were included in the database. Myelosuppression lasting 42 days or more was reported as a serious adverse event. As shown in Table 15, the most frequently reported SAEs in the CML safety cohort were primarily myelosuppressive events. Disease progression was reported in 7.6% of patients. All other events occurred in less than 5% of patients.

Table 15. Serious Adverse Events in ≥ 2% of Patients in Studies CML-202 and CML-203

Serious Adverse Event	CML-CP n = 70	CML=AP n -= 36	CML-BP n = 25	Total (n = 131)
Number (%) of patients with at least one SAE	38 (54.3%)	19 (52.8%)	21 (84.0%)	78 (59.5%)
Febrile neutropenia	5 (7.1%)	5 (13.9%)	4 (16.0%)	14 (10.7%)
Thrombocytopenia	10 (14.3%)	2 (5.6%)	2 (8.0%)	14 (10.7%)
Bone marrow failure	10 (14.3%)	0	0	10 (7.6%)
Disease progression	2 (2.9%)	2 (5.6%)	6 (24.0%)	10 (7.6%)
Anemia	2 (2.9%)	3 (8.3%)	0	5 (3.8%)
Febrile bone marrow aplasia	3 (4.3%)	1 (2.8%)	0	4 (3.1%)
Pyrexia	3 (4.3%)	0	2 (8.0%)	5 (3.8%)
Sepsis	1 (1.4%)	2 (5.6%)	1 (4.0%)	4 (3.1%)
Neutropenia	2 (2.9%)	1 (2.8%)	0	3 (2.3%)
Pancytopenia	2 (2.9%)	1 (2.8%)	0	3 (2.3%)
Diarrhea	0	3 (8.3%)	1 (4.0%)	4 (3.1%)
Pneumonia	1 (1.4%)	1 (2.8%)	1 (4.0%)	3 (2.3%)
Transfusion reactions	1 (1.4%)	1 (2.8%)	1 (4.0%)	3 (2.3%)

9.4 Deaths

Deaths that occurred on study, within 30 days of discontinuing study, and during follow-up for ongoing AEs at the time of study discontinuation were reported and included in the database. Of the 131 patients in the CML safety cohort, 27 (20.6%) died as of the data cut-off date (September 17, 2009) (Table 16). Sixteen of these death occurred within 30 days after the last dose of study medication (4 CML-CP, 4 CML-AP, and 8 CML-BP). All but five of the deaths were considered to be unrelated to study treatment, and in many cases, the cause of death was attributed to the patients' underlying disease or its complications.

Table 16. Listing of Patient Deaths in Studies CML-202 and CML-203

Study	Pt Number	Sex	Age	Primary Cause of Death
Relationship: Related to study drug or of unknown causality				
CML-CP				
CML-202	009/003	F	57	unknown
CML-202	029/001	M	63	sepsis
CML-AP				
CML-202	020/004	M	83	sepsis
CML-203	350/001	F	56	febrile neutropenia
CML-BP				
CML-202	002/001	M	49	sepsis
Relationship: Unrelated to study drug				
CML-CP				
CML-202	009/001	M	62	cerebral hemorrhage
CML-202	025/001	M	72	bone marrow necrosis
CML-202	030/003	F	78	pyrexia
CML-202	040/001	M	67	deep vein thrombosis
CML-202	071/004	F	40	cerebral hemorrhage
CML-203	330/001	M	68	chronic myeloid leukemia
CML-AP				
CML-202	006/001	M	67	chronic renal failure
CML-202	030/001	F	64	pneumonia
CML-202	050/001	F	44	death
CML-203	321/001	M	57	disease progression
CML-BP				
CML-202	001/004	M	49	pneumonia
CML-202	006/004	M	53	arrhythmia
CML-202	006/005	F	19	pulmonary hemorrhage
CML-202	006/007	M	61	disease progression
CML-202	022/001	F	23	leukostasis
CML-202	071/001	F	28	tumor lysis syndrome
CML-203	301/018	F	64	disease progression

continued

Study	Pt Number	Sex	Age	Primary Cause of Death
CML-203	302/001	M	62	sepsis
CML-203	305/001	M	45	disease progression
CML-203	305/002	M	30	disease progression
CML-203	360/003	F	48	disease progression
CML-203	360/005	F	58	disease progression

9.5 Dose Adjustments and Modifications

Dose modification consisted of a reduction in the number of dosing days per cycle. Adjustments to the dose per injection (1.25 mg/m^2) were not made. Dose delays in studies CML-202 and CML-203 were commonly due to myelosuppression and were more frequently experienced in the early treatment cycles when patients were receiving the more intensive 14 day dosing schedule (Table 17). The length of delays between cycles generally declined with each cycle. The primary causes of delays transitioned from being predominantly hematologic toxicities in the initial cycles, to being logistical issues (such as patient availability) in the later cycles.

Table 17. Dose Delays by Cycle in Studies CML-202 and CML-203

	Cycle 2 n=109	Cycle 3 n=90	Cycle 4 n=75	Cycle 5 n=63	Cycle 6 n=51	Cycle 7 n=44	Cycle 8 n=32	Cycle 9 n=29	Cycle 10 n=28	Cycle 11 n=24	Cycle 12 n=19
Number of patients with delays (%)	49 (45.0)	51 (56.7)	49 (65.3)	33 (52.4)	22 (43.1)	22 (50.0)	11 (34.4)	13 (44.8)	8 (28.6)	7 (29.2)	5 (26.3)
Duration of delays (days) (range)	12 (1-109)	25 (2-184)	12 (1-74)	11 (1-52)	5 (1-38)	11 (1-49)	11 (2-26)	5 (1-39)	4 (2-17)	4 (1-6)	5 (2-11)
Reasons for delay [n (%) of events[a]]	50	53	50	35	22	23	11	13	9	7	5
Thrombocytopenia (%)	12 (24.0)	25 (47.2)	13 (26.05)	5 (17.1)	5 (22.7)	7 (34.7)	3 (27.3)	4 (30.8)	1 (1.1)	2 (28.6)	2 (40.0)
Neutropenia (%)	12 (24.0)	8 (15.1)	8 (16.0)	6 (17.1)	2 (9.1)	3 (13.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
Pancytopenia (%)	13 (26.0)	10 (20.8)	8 (16.0)	2 (5.7)	3 (13.6)	3 (13.0)	2 (18.2)	1 (7.7)	1 (11.1)	1 (14.3)	0 (0.0)
Patient availability[b] (%)	8 (16.00)	6 (11.3)	10 (20.0)	9 (25.7)	7 (31.8)	4 (17.4)	3 (27.3)	7 (53.8)	6 (66.7)	5 (57.1)	1 (20.0)
Other (%)[c]	5 (10.0)	3 (5.7)	11 (22.0)	12 (34.3)	5 (22.7)	5 (21.7)	3 (27.3)	1 (7.7)	1 (1.0)	0 (0.0)	1 (20.0)

[a] Patients may have had more than one reason for delay per cycle
[b] Includes scheduling, availability, and logistic reasons
[c] Includes other adverse events, other required procedure, and no reason recorded

9.6 Safety Conclusions

Omacetaxine treatment is generally well tolerated and associated with a predictable and manageable myelosuppression profile that has been well-characterized in a broad range of heavily pretreated patients, including the largest prospectively designed trial of CML patients with the T315I mutation. Overall, SC omacetaxine twice daily dosing of 1.25 mg/m^2 was well tolerated by patients in the pivotal and supportive CML studies. The most common adverse events were related to myelosuppression, a recognized complication of CML therapy and an anticipated adverse event in heavily pretreated patients. Nadir values were typically reached within 2 to 3 weeks after the first dose of each cycle, and recovery of blood counts generally occurred within 1 to 3 weeks of the nadir. Dose delays occurred more frequently during the early intensive treatment cycles and were managed by adjustment of the number of dosing days per treatment cycle. Non-hematologic toxicities were less common and generally mild to moderate in severity. A detailed analysis of safety data did not reveal a concern regarding cardiac toxicity with the SC administration of omacetaxine. Consistent with the poor prognosis of the CML T315I patient population, most deaths were attributed to disease progression. Five deaths were attributed by the investigators to drug; four of these were due to infection. In conclusion, the subcutaneous administration of omacetaxine has been well characterized with a predictable and manageable safety profile in CML T315I patients.

10 SELF ADMINISTRATION

Omacetaxine is intended to be self-administered at home by the patient or caregiver and requires reconstitution with normal saline (sodium chloride injection, USP, 0.9%) prior to administration. The drug is supplied as a kit that includes a vial of lyophilized omacetaxine, a vial of sterile saline, and the syringes and needles needed for reconstitution and administration.

The potential for reconstitution, dosing, or injection errors did exist in the clinical studies; however, analysis of the data available on over 25,000 individually administered doses indicates that errors are very rare. There have not been any reported adverse events as a result of the inappropriate or incorrect reconstitution and/or administration of SC omacetaxine. One patient injected two times the intended dose on one occasion without incident.

In studies CML-202 and CML-203, French patients received omacetaxine injections prepared and administered at home by a health care professional, while patients in the rest of the world (ROW) self-administered the study drug. Therefore, it was possible to conduct an analysis to compare the data from patients in France to the ROW. This analysis showed that injection site reactions occurred with similar frequency in both the French and ROW groups (37.1% and 31.3%, respectively), and all events were mild to moderate in severity.

Overall, there was no discernable difference in the local tolerability of omacetaxine based on the method of administration (health care professional versus self administration).

11 RISK EVALUATION AND MANAGEMENT STRATEGY

ChemGenex has proposed a Risk Evaluation and Management Strategy (REMS) with the goals of 1) informing patients and treating physicians of the potential risks from the use of omacetaxine, 2) minimizing the risk of self-administration injection errors with omacetaxine, and 3) monitoring the long-term safety and safe use of omacetaxine.

The proposed REMS will consist of the following:

- Medication guide: The medication guide will provide detailed instructions for the patient/caregiver on the safe practices for administration of omacetaxine.
- Communication plan: The communication plan will be targeted to oncologists, visiting nurses, and other health care practitioners who will be prescribing omacetaxine and treating patients on the drug, and will include the following materials:
  - Approved package insert and Medication Guide
  - Dear Healthcare Professional Letter
  - OMAPRO.com website
  - Educational and training materials for patients and nurses
  - Instructional materials for training on safe practices for dosing, administration, and disposal
  - Instructional video on self-administration by subcutaneous injection
  - Information on proper use of accessory supplies, including gloves, goggles, and drapes that will be used during the preparation and administration of drug

There will also be an ongoing assessment of the REMS to monitor the effectiveness of patient and prescriber understanding and compliance in the usage of the product.

12 BENEFIT/RISK EVALUATION

The Bcr-Abl T315I kinase domain mutation is the most common mutation identified in CML patients who have failed TKI therapy. Patients with this mutation do not respond to therapy with any of the currently available TKIs. The life expectancy of these patients is considerably reduced compared to TKI responders and they therefore have an urgent unmet medical need for a proven and effective therapy.

Treatment with subcutaneously administered omacetaxine is effective in heavily pre-treated patients with CML who have the T315I mutation. Patients with this mutation who were in CML-CP at the time of treatment achieved durable hematologic and cytogenetic responses. In addition the median overall survival of these patients in study CML-202 exceeded that reported in the literature[37-39]. Patients with advanced disease achieved high rates of CHR which is considered a valuable endpoint that is predictive of clinical benefit[3-5]. Similar and supportive efficacy results were also seen in study CML-203, which assessed the effectiveness of omacetaxine in CML patients who had failed two or more TKIs.

Omacetaxine has a manageable safety profile comprised primarily of predictable and reversible myelosuppression. Myelosuppression is a common effect of any anti-leukemic agent and is more frequent in patients who have been pre-treated with multiple therapies. Following treatment with omacetaxine, nadir values were typically reached within 2 to 3 weeks after the first dose of each cycle, and recovery of blood counts generally occurred within 1 to 3 weeks of the nadir. In clinical practice, physicians are experienced in modifying doses and duration of treatment according to blood levels of neutrophils and platelets. Myelosuppression was expected in such a cohort and planned for in the trial designs. As a result, adjustment of dosing days, rather than change in dosage, was utilized successfully during the clinical studies to manage toxicities.

The most common non-hematologic toxicities (diarrhea, fatigue, pyrexia, nausea, and asthenia) were generally mild to moderate in severity and typically not dose-limiting.

SC omacetaxine was safely administered by the patient at home without direct medical supervision. Patient self administration versus administration by a health care professional showed no discernable meaningful differences in tolerability, and injection complications were limited to mild site reactions.

The clinical experience describes a favorable benefit/risk profile for omacetaxine in the proposed indication. A REMS has been proposed to help ensure that the safe, effective, and convenient self administration experience from the clinical trials is translated to the post approval setting. Additional labeling recommendations call for routine monitoring of blood counts to appropriately track clinical effects and for the management of dosing adjustments to maintain the benefit/risk balance.

Given the favorable benefit/risk profile for omacetaxine in adult CML patients who have the Bcr-Abl T315I mutation and have failed imatinib therapy, omacetaxine offers the only therapeutic treatment alternative for a patient population with a poor prognosis and no proven treatment options.

13 ABBREVIATIONS

AE	adverse event
AML	acute myelogenous leukemia/acute myeloid leukemia
ANC	absolute neutrophil count
Ara-c	arabinoside-c, cytarabine
ATP	adenosine triphosphate
ATU	Autorisations Temporaires d'Utilisation
AUC	area under the curve
Ba/F3	murine bone marrow derived cell line
Bcr-Abl	breakpoint cluster region-Abelson
CCyR	complete cytogenetic response
CHR	complete hematologic response
CI	confidence interval
CL	clearance
CL/F	(apparent) clearance
C_{max}	maximum concentration
CML	chronic myelogenous leukemia/chronic myeloid leukemia
CML-AP	chronic myeloid leukemia, accelerated phase
CML-BP	chronic myeloid leukemia, blast phase
CML-CP	chronic myeloid leukemia, chronic phase
CTC	Common Terminology Criteria
CV	coefficient of variation
4′-DMHHT	demethyl homoharringtonine, DMHHT
DMC	Data Monitoring Committee
ECG	electrocardiograph, electrocardiogram
hERG	human ether-á-go-go related gene
HHT	homoharringtonine
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplant
HU	hydroxyurea
IFN-α	interferon
IND	Investigational New Drug
IV	intravenous, intravenously
L	liter
m	meter
MCyR	major cytogenetic response
Mcl-1	myeloid cell leukemia 1
mg	milligram

mL	milliliter
msec	millisecond
MTD	maximum tolerated dose
MU	mega units
NaCL	sodium chloride
NCI	National Cancer Institute
NDA	New Drug Application
NEL	no evidence of leukemia
ng	nanogram
ODAC	Oncologic Drugs Advisory Committee
OM	omacetaxine mepesuccinate
PCyR	partial cytogenetic response
P-gp	p-glycoprotein
Ph	Philadelphia chromosome
PK	pharmacokinetics
qRT-PCR	quantitative reverse transcription polymerase chain reaction
QT	Q-T interval (the time between start of Q wave and end of T wave in heart's electrical cycle)
QTc	corrected Q-T interval
QTcB	corrected Q-T interval using Bazett's correction formula
QTcF	corrected Q-T interval using Fridericia's correction nformula
RCP	return to chronic phase
REMS	Risk Evaluation and Management Strategy
ROW	rest of the world
SAE	serious adverse event
SC	subcutaneous, subcutaneously
SD	standard deviation
$t_{1/2}$	half life
T315I	threonine 315 Isoleucine
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
t_{max}	time at which maximum plasma concentration is reached after drug administration
USP	United States Pharmacopeia
Vz/F	(apparent) volume of distribution
WBC	white blood cell

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